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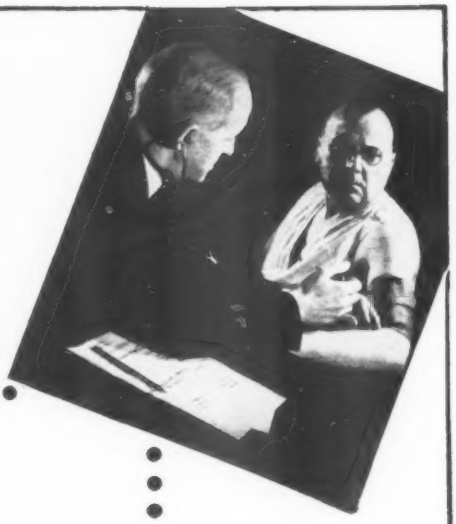

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1949

## ORIGINAL ARTICLES

# RAPID ATTAINMENT OF THERAPEUTIC PENICILLIN CONCENTRATIONS IN THE CEREBROSPINAL FLUID

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The complications observed following the intrathecal administration of penicillin[8,14,19,20] justify a re-evaluation of the possibility of attaining therapeutically significant penicillin concentrations in the cerebrospinal fluid following parenteral administration. It is generally stated that the blood-brain barrier hinders the free exchange of penicillin between the plasma and the cerebrospinal fluid but the support for this statement comes from investigations carried out with smaller doses of penicillin than are currently in wide use. It has been suggested that larger doses of penicillin might cause diffusion into the cerebrospinal fluid but few data are available to substantiate this supposition.

Measurable quantities of penicillin have been observed in the cerebrospinal fluid following its parenteral administration. Ten to 25 million units given by continuous intravenous infusion[18] and 100,000 units intramuscularly every 3 hours[2] have given rise to comparable penicillin concentrations in the cerebrospinal fluid of those patients in whom diffusion of the antibiotic from plasma to subarachnoid space occurred. Neither of these investigations have answered the question of how soon after the initial administration of penicillin the drug is demonstrable in the cerebrospinal fluid. In this paper we present data indicating that penicillin can be found in the cerebrospinal fluid 2 and 3 hours after a single intravenous injection of penicillin.

**Patients studied.** Twenty-one patients suffering from central nervous system syphilis (paresis) were studied. These patients were not selected in any way and apart from their neurological disease were in good or fair general health.

**Method of Study.** Because a review of the literature indicated the likelihood of failure to obtain assayable quantities of penicillin in the cerebrospinal fluid of normal patients un-

less a blood concentration of 10 to 30 units per cc. of plasma was attained for some length of time, commonly used doses of penicillin (20,000 to 50,000 units every 3 hours) were not employed in this study. A single intramuscular dose of 500,000 units of penicillin will give plasma concentrations above 12 units per cc. for at least 30 minutes[13] and

TABLE I.—PENICILLIN CONCENTRATIONS IN PLASMA AND CEREBROSPINAL FLUID AFTER INTRAVENOUS INJECTION OF 500,000 UNITS WITH AND WITHOUT 3 GM. CARONAMIDE INTRAVENOUSLY.

| PATIENT | CARONAMIDE | PENICILLIN CONCENTRATIONS* | | | | |
|---|---|---|---|---|---|---|
| | | BLOOD | | | CSF | |
| | | 5 min. | 2 hrs. | 3 hrs. | 2 hrs. | 3 hrs. |
| | | (after penicillin) | | | (after penicillin) | |
| GROUP I | | | | | | |
| LR | - | 70.90 | 1.08 | .416 | .023 | .045 |
| NT | - | 70.90 | 4.32 | 2.160 | 0 | .023 |
| JM | - | X | 2.88 | .496 | .023 | .045 |
| AVER. PENICILLIN | | 70.90 | 2.78 | 1.024 | .015 | .037 |
| GROUP II | | | | | | |
| JM | - | 23.81 | .992 | .124 | .031 | .021 |
| | + | 95.23 | 1.98 | .496 | .062 | .062 |
| RR | - | 67.58 | .248 | .124 | .031 | .031 |
| | + | 184.32 | 8.64 | 4.32 | .045 | .045 |
| JS | - | 70.92 | 1.08 | .416 | .045 | .045 |
| | + | X | 5.76 | 2.16 | .090 | .045 |
| AJ | - | 70.92 | 1.44 | .416 | .045 | .023 |
| | + | 95.23 | 2.98 | .992 | .026 | .093 |
| MW | - | 46.08 | .720 | .416 | 0 | .023 |
| | + | 47.62 | 1.98 | 1.15 | .016 | .031 |
| TJ | - | 34.56 | X | 1.08 | .023 | .045 |
| | + | 63.49 | 2.11 | .992 | .031 | .031 |
| WW | - | 63.49 | 1.49 | .744 | .045 | .023 |
| | + | 63.49 | 7.94 | 2.97 | .062 | .095 |
| SF | - | 31.44 | .744 | .248 | .023 | 0 |
| | + | 69.12 | 2.88 | 1.08 | .045 | .023 |
| BC | - | 63.49 | .992 | .248 | .045 | .045 |
| | + | 63.49 | 5.95 | .999 | .062 | .062 |
| FMcL | - | 31.74 | .496 | .186 | 0 | .023 |
| | + | 137.52 | 2.16 | 1.08 | .045 | .023 |
| JO | - | 46.08 | .744 | .124 | 0 | 0 |
| | + | 137.52 | 4.32 | 1.08 | .023 | .023 |
| RM | - | 31.74 | .992 | .248 | .023 | 0 |
| | + | 137.52 | 8.64 | 2.88 | .045 | .045 |
| HZ | - | 63.49 | 1.98 | 1.08 | .045 | .045 |
| | + | 137.52 | 11.52 | 5.76 | .045 | .090 |
| MK | - | 31.74 | 1.49 | .496 | .090 | .045 |
| | + | 34.56 | 5.74 | 2.50 | .135 | .135 |
| GG | - | 63.40 | 1.98 | .496 | .023 | .023 |
| | + | 69.12 | 5.74 | 2.50 | .022 | .045 |
| AVER. PENICILLIN | | 49.37 | 1.10 | .430 | .031 | .026 |
| AVER. PENICILLIN + CARONAMIDE | | 95.41 | 5.22 | 2.08 | .050 | .056 |
| GROUP III | | | | | | |
| DG | + | 137.52 | 2.88 | 1.08 | .023 | .023 |
| TW | + | 47.62 | 1.98 | .744 | .031 | .031 |
| AC | + | 92.16 | 2.88 | 1.44 | .045 | .023 |
| AVER. PENICILLIN + CARONAMIDE | | 92.43 | 2.58 | 1.088 | .033 | .025 |

* Penicillin proven by inhibition with penicillinase; penicillin measured in units per cc.

the same dose introduced intravenously will give peak concentrations of between 30 and 70 units per cc. and above 10 units per cc. for 30 minutes. The intravenous route of administration was employed in order to obtain the advantage of a brief but high penicillin plasma concentration immediately after administration that might favor diffusion across the blood-brain barrier. Penicillin in aqueous solution (500,000 units) was given intravenously (injection time being 7 to 15 seconds) and thereafter blood specimens were obtained at 5 minutes, 2 hours and 3 hours. In addition, 2 and 3 hours after therapy with penicillin, lumbar puncture was performed with a 21 gauge needle and the cerebrospinal fluid specimens obtained for penicillin assay. Blood and cerebrospinal fluid specimens were assayed for penicillin by a modified Rammelkamp serial dilution method employing a Group A hemolytic streptococcus as the test organism. Three patients (Table 1, Group I) were studied in the above manner following the administration of 500,000 units of penicillin alone and 3 patients (Table 1, Group III) received the same dose of penicillin and 3 gm. of caronamide intravenously in aqueous solution. An additional 15 patients (Table I, Group II) were investigated twice, once after the intravenous administration of 500,000 units of penicillin alone and again after the intravenous administration of 500,000 units of penicillin together with 3 gm. of caronamide. The same schedule of sampling of the blood and cerebrospinal fluid was followed in the two periods of study. Each patient was his own control and intervals of 7 to 27 days intervened between the two periods of study.

**Results.** The results obtained in this study are presented in Table 1. The administration of 500,000 units of penicillin in aqueous solution resulted in demonstrable concentrations of penicillin in the cerebrospinal fluid at 2 hours in 14 of 18 individuals, and at 3 hours in 15 of 18 persons (Groups I and II). When the same dose of penicillin was administered with 3 gm. of caronamide, penicillin appeared in the cerebrospinal fluid at 2 and 3 hours in all of the 18 patients (Groups II and III). The plasma concentrations resulting from the administration of penicillin were enhanced by caronamide from 2 to 5 times, and the cerebrospinal fluid concentrations were doubled. The caronamide concentrations observed in the plasma after the intravenous administration of 3 gm. of the drug were adequate to inhibit penicillin excretion by the renal tubules.[3]

The results obtained in the group of 15 patients (Group II) studied as their own controls in both phases of the investigation were statistically analyzed and it was found that the difference in plasma and cerebrospinal fluid penicillin concentrations as a result of the administration of caronamide were highly significant ($p=0.02$-$0.05$). The difference observed between the 2 and 3 hour determinations of penicillin in the cerebrospinal fluid were not significant either when penicillin alone or penicillin in conjunction with caronamide were administered.

**Discussion.** The complications that have been reported as due to intrathecal injection of penicillin may indeed have been due to the drug, but it seems reasonable to concede the possibility that some of the complications have been due to the disease treated. Furthermore, the use of penicillin less refined than that currently available and the use of unnecessarily large doses may have accounted for some of the results attributed to intrathecal injection of the antibiotic. Nevertheless, if it could be established that penicillin can, with regularity, be demonstrated in the cerebrospinal fluid following parenteral administration, intrathecal administration might be limited to a relatively few patients presenting definite indications for this route of injection.

Any particular concentration of penicillin has little meaning from a therapeutic standpoint unless it is interpreted in terms of both the sensitivity of the organism producing the infection under treatment and the defense

mechanisms of the host in whom the infection is being treated. Wide recognition has been given, however, to a penicillin concentration of 0.03 unit per cc. as being "therapeutically significant" because this amount of the antibiotic "is adequate to sterilize actively growing cultures of almost all strains of gonococcus, Group A hemolytic streptococcus, pneumococcus and most strains of alpha hemolytic streptococcus, about half of the strains of meningococcus, and a somewhat smaller proportion of strains of pathogenic staphylococci".[15]

Penicillin concentrations of this magnitude have been observed in the cerebrospinal fluid of persons suffering from central nervous system syphilis following the administration by continuous intravenous drip of 10 to 25 million units during a 24 hour period, but only when doses of 20 to 25 million units were so administered were these amounts of penicillin demonstrated in all patients.[18] Comparable penicillin concentrations in the cerebrospinal fluid were observed in similar patients following the administration of 100,000 units intramuscularly at intervals of 3 hours,[2] but in only 18 of 23 patients when penicillin alone was given and only 20 of 25 patients when penicillin was given in conjunction with caronamide. Apart from these reports the consensus is that either no penicillin or only a small amount in an occasional patient[7,9,10,12,16] crosses the hematoencephalic barrier of a normal person. There is precedent in the medical literature for regarding paretics as having "normal" barriers between the plasma and cerebrospinal fluid,[11,18] and there is good evidence to believe that the inflamed tissues interposed between plasma and cerebrospinal fluid offer less impediment to the passage of penicillin than those not so involved.[5,11,17]

In view of the greater permeability of an inflamed hematoencephalic barrier[11] there is every reason to believe that an amount of penicillin in the plasma that will cause diffusion of measurable quantities of drug into the cerebrospinal fluid of normal patients (paretics) will cause diffusion of even greater amounts in patients with meningitis. It should be emphasized, however, that before the results of an investigational study are applied to therapy, the schedule of penicillin therapy employed should offer reasonable assurance that the diffusion of significant quantities of penicillin into the cerebrospinal fluid will occur in all normal individuals. The demonstration of assayable quantities of penicillin in the cerebrospinal fluid of even a few patients following parenteral penicillin is of academic interest but unless it can be shown that significant amounts of penicillin can be observed in 100% of patients so treated, it would be hazardous to rely entirely upon parenterally administered penicillin for the treatment of meningitis.

One hundred thousand units intramuscularly every 3 hours, either alone or given in conjunction with caronamide,[2] failed to fulfill this criterion, and so also have 10 and 15 million units administered by continuous intravenous drip for 24 hours.[18] Since these 2 schedules of penicillin dosage resulted in plasma penicillin concentrations of at least 10 units per cc. for variable periods of time in the case of the intramuscularly administered penicillin, and rather constantly in the case of the infused penicillin, it may be judged that these plasma concentrations of penicillin cause diffusion into the cerebrospinal fluid in some, but not all, patients. Therefore, an intravenous dose of penicillin was chosen for this study that would result in fleeting concentrations of from 30 to 70 units (average 49.64) units per cc. above 10 units for approximately 30

minutes[13] and above 1 unit for 2 hours. Attention is directed to the plasma concentrations existing at specific time intervals after the injection of the single dose of penicillin employed in this study because it is probable that there is a considerable lag between the time that penicillin first diffuses into the cerebrospinal fluid and the time that it is detected in the lumbar cerebrospinal fluid. Any delay in the appearance of penicillin in the lumbar cerebrospinal fluid is of importance in the treatment of meningitis. The appearance of penicillin in the cerebrospinal fluid within 2 hours after the initiation of therapy would be highly desirable and, if demonstrated, could be considered "prompt treatment" at the site of infection.

An interval of 2 hours after penicillin injection was arbitrarily chosen for sampling of the cerebrospinal fluid. Patients NT, MW and RMcL (Table 1) failed to show penicillin in the spinal fluid at 2 hours, but it was detected at 3 hours. Patient JC had no measurable penicillin in the spinal fluid at either 2 or 3 hours. Thus, 3 of the 4 patients who failed to show penicillin in the cerebrospinal fluid at the end of 2 hours did show it at 3 hours, the fourth case showing penicillin at neither of these times. In only 2 cases was the reverse true (SF, RM), penicillin being demonstrated at 2 hours and not at 3 hours. It seems probable, therefore, that the interval of 2 hours approximates rather closely the time required for the appearance of penicillin in the lumbar cerebrospinal fluid after the intravenous administration of 500,000 units of penicillin. More extensive sampling of the cerebrospinal fluid to determine the disappearance time of penicillin from the subarachnoid space was not done.

When the same dose of penicillin (500,000 units) was administered intravenously in conjunction with 3 gm. of caronamide, the resulting penicillin plasma concentrations were enhanced so that transitory penicillin concentrations of from 60 to 104 units per cc. (average 95 units per cc.), above 5 units per cc. for 2 hours and above 2 units per cc. for 3 hours were reached in the average patient. These elevated concentrations of penicillin in the plasma resulted in doubling the amounts of penicillin demonstrated in the cerebrospinal fluid, and it can be observed that, in the 18 patients to whom the combination of drugs was administered, all showed penicillin in the spinal fluid at 2 and 3 hours. In an additional group of 25 patients penicillin appeared in the lumbar spinal fluid within 1 hour in every patient to whom 500,000 units of penicillin and 3 gm. of caronamide were given intravenously. Statistical analysis shows that the likelihood of the added elevations of penicillin in the spinal fluid following the combined use of penicillin and caronamide being due to chance alone is between 1 to 100 and 1 to 1000.

Clearly the elevation of penicillin concentrations in the plasma by the use of caronamide increased diffusion of penicillin into the cerebrospinal fluid, but it should be emphasized that the same results could be obtained without the aid of caronamide if sufficient penicillin was employed to give the same magnitude of penicillin plasma concentrations. Caronamide increased the penicillin plasma concentrations resulting from 500,000 units of penicillin from 2 to 5 times, these results conforming to those previously reported.[1,6] The intravenous administration of 3 gm. of caronamide was accompanied by no manifestations of toxicity, but about half the patients experienced a transitory generalized sensation voluntarily described as "itching". The rapidity of injection of a 15% solution of caronamide is the

most obvious explanation of this observation.

The amounts of penicillin observed in the cerebrospinal fluid were therapeutically significant, but perhaps minimal from the standpoint of relying upon them for the treatment of a purulent meningitis amenable to penicillin therapy. However, it should be stated that many systemic infections are treated without either attaining or maintaining in the plasma penicillin concentrations as high as those here observed in the cerebrospinal fluid. Since these levels were attained in the cerebrospinal fluid of normal individuals in whom the barrier between the blood and cerebrospinal fluid was less permeable than is the case in patients suffering from meningitis, much higher concentrations of penicillin might be anticipated in patients having inflammation of the meninges. This has proven to be the case in meningitis patients already studied and to whom 500,000 units of penicillin have been given intravenously. Penicillin concentrations in the cerebrospinal fluid as high as 2 to 8 units per cc. have been observed within 2 hours after the first injection of penicillin.[4]

**Conclusions.** In a series of 21 patients who had uninflamed meninges, it has been shown that penicillin diffuses into the cerebrospinal fluid within 2 hours after a single intravenous injection of 500,000 units of penicillin. Three patients failing to show diffusion of the antibiotic into the cerebrospinal fluid after the intravenous administration of 500,000 units, showed measurable quantities of penicillin in the cerebrospinal fluid when caronamide was administered intravenously in conjunction with the same dose of penicillin. The observation that therapeutically significant levels of penicillin were attained in the cerebrospinal fluid in all of the patients here studied suggests that the parenteral and particularly intravenous administration of penicillin has a place in the therapy of purulent meningitis and that intrathecal injection of penicillin is unnecessary in the majority of patients.

The authors are indebted to the chiefs of the Neurological Services of the Philadelphia General Hospital for permission to study patients on their services, to Miss June Heckman for penicillin assays reported in this study, and to Mr. J. L. Ciminera for statistical analysis of data.

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# EFFECTIVE PENICILLIN THERAPY IN SUBACUTE BACTERIAL ENDOCARDITIS AND OTHER CHRONIC INFECTIONS

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Empiric methods are generally used as a guide for determining penicillin therapy. These range from arbitrary dosage schedules for certain infections to correlation of *in vitro* sensitivity of the etiologic organism with blood levels obtained during therapy as determined by assay with an unrelated species or strain of organism. These methods usually give therapeutically satisfactory results with highly sensitive organisms, but are often unsatisfactory when relatively resistant strains of bacteria are encountered.

To meet this deficiency, the technic of assaying the bacteriostatic activity of a patient's serum level during penicillin therapy with the isolated etiologic organism was introduced. This technic was initially developed in the course of studies of subacute bacterial endocarditis due to resistant strains of alpha hemolytic streptococci.[3] The success obtained in our hands has led to our use of this technic as a guide to effective therapy in septicemias secondary to a variety of acute and chronic suppurative conditions with satisfactory results. Its simplicity should make it practical for the small bacteriological laboratory, since for therapeutic purposes the standard assay may be omitted. This report deals with the work done in establishing the validity of this technic.

**Methods.** Recently isolated organisms are subcultured to 2 or 3 suitable agar slants at the time the original sensitivities are determined, and stored at 4°C. for the duration of therapy for reference. Following determination of the sensitivity of the isolated strain, a dosage schedule is inaugurated to attain a minimum blood level of at least 4 times the indicated sensitivity. Calculations are based on the average levels found at stated intervals for standard dosages and methods of administration of the various penicillin preparations currently available.** Usually 24 hours are allowed to elapse for stabilization of initial irregularities in absorption and excretion rate. When the intermittent method of administration is employed, adequate blood samples are aseptically drawn at the low point of the blood concentration curve, *i. e.*, about 5 minutes before the next injection time.

The direct penicillin assay test is carried out as follows: Serial 2-fold dilutions of the patient's serum in broth are made in 8 sterile tubes ranging from undiluted to 1:128. A ninth tube, containing broth diluent only, serves as a control. The organism, isolated from the patient, previously grown in suitable broth for 6 to 18 hours at 37°C., or until the turbidity of the culture is equivalent to a concentration of approximately 600 million bacteria per cc., is used. We have found that total quantities of 1 cc. per tube with an inoculum of 0.05 cc. of approximately 1:1000 dilution of the isolated organism

* These departments are supported in part by the Michael Reese Research Foundation.

** In general, to maintain a level of 1 Oxford unit per ml. of serum, 1 million units by continuous drip (IV) or 1.5 to 2 million units by intermittent intramuscular injection are required. Caronamide and p-amino hippuric acid have both been successfully used to obtain elevated serum concentrations.

are convenient for pipetting and reading. After incubation at 37°C. for 18 hours, the highest dilution completely inhibiting growth is recorded. When micro-aerophilic or obligate anerobic bacteria are encountered, the tubes are incubated under anerobic conditions. The dosage is then adjusted in accordance with results obtained in the direct test. A re-check should be made 24 hours after any change in the therapeutic regimen.

INTERPRETATION OF TEST. Complete inhibition of growth in the first tube (undiluted serum) and slight growth in the second (1:2 dilution) is interpreted as the minimum satisfactory dosage which will be effective for the patient concerned and the specific organism involved. This concentration of penicillin has proven to be therapeutically satisfactory in our hands when maintained for considerable periods of time.

Since the bactericidal rate has frequently been found to be greatly accelerated at penicillin concentrations slightly higher than that resulting in complete bacteriostasis, we feel that a penicillin serum level producing complete inhibition in the first 2 tubes represents the optimal dosage to be maintained for the duration of either bacteriological or clinical evidence of active infection.

Inhibition at higher dilutions indicates that penicillin in excess of the optimal requirement is being administered, and the intervals or the number of units per injection may be regulated accordingly. We feel that any evidence of growth in the first tube indicates that the level is inadequate and should be at least doubled immediately despite previously ascertained sensitivity.

As evidenced by the Tables appended, this type of planned therapy, insuring serum levels sufficiently high to be completely bacteriostatic for the patient's own organism, has proved eminently satisfactory in the management of subacute bacterial endocarditis as well as in the control of various other infections. In fact, not a single case of streptococcic endocarditis has failed to respond with complete clinical cure which we have treated in this manner during the past two years.

Table 1 presents the results of controlled therapy in 10 unselected cases of subacute bacterial endocarditis due to the *Streptococcus viridans* group treated at Michael Reese Hospital during the past 28 months. Clinical and bacteriological evidence of complete arrest were obtained in all but one of the early cases (Case 2) which was treated with inadequate amounts of penicillin. All patients were followed after discharge by periodic blood cultures for at least a year, and all have remained entirely symptom free to date. Thirty-four tests were performed in these 10 cases to establish the validity of these criteria of effective therapy. The amount of penicillin required for blood serum bacteriostasis varied from 1 to 32 times the broth concentration necessary as determined by direct assay. Some variation in the ratio in successive tests on the same patient was observed. Our impression is that these findings are more apparent than real because they may well be explained on the basis of the sources of error inherent in the serial dilution method of assay. Each reading actually represents a range, rather than an exact number, of units of penicillin. Case 5, which was followed over a longer period, however, shows a consistent slow drop in the ratio which suggests that a rising antibody titer may have had an enhancing effect.

Difficulty in obtaining adequate amounts of penicillin is largely responsible for fluctuations in levels of earlier cases. Not all dosage schedules were reduced to the minimum effective level, although uniform success with those which were decreased would indicate that others had been maintained

TABLE I.--PENICILLIN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS DUE TO ALPHA HEMOLYTIC STREPTOCOCCI

| Case | Date | Standard Turbidity Test | | Direct test with Patient's Organism | | | | | | | | Ratio of Effective level of Sensitivity | Result of Therapy: |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sensitivity (in Oxford units) | Serum level (Oxford units/ml.) | Serum Dilutions | | | | | | | | | |
| | | | | Undil. | 1:2 | 1:4 | 1:8 | 1:16 | 1:32 | 1:64 | 1:128 | | Duration |
| 1. R.B. | 10/20/45 | 5.0 I | 10.24 | + | + | + | + | + | | | | | |
| | 11/11/45 | | 12.80 | ± | + | + | + | + | | | | | |
| | 11/27/45 | 5.0 II | 40.96 | 0 | 0 | + | + | + | | | | 4:1 | Clinical cure: |
| | 1/14/46 | | 5.12§ | + | + | + | + | + | | | | | 2 yrs. 8 mos. |
| 2. H.B. | 2/12/46 | 5.0 I | 25.60 | 0 | 0 | + | + | + | | | | 2.5:1 | |
| | 2/27/46 | | 2.56 | not done | | | | | | | | | |
| | 3/5/46 | | 40.96 | 0 | 0 | 0 | 0 | + | | | | 1:1 | |
| | 3/14/46 | | 25.60 | 0 | 0 | + | + | + | | | | 2.5:1 | |
| | 3/22/46 | | 1.28 | + | + | + | + | + | | | | | |
| | 3/29/46 | 8.75 III | 40.96 | 0 | 0 | 0 | + | + | | | | 1:1 | |
| | 4/1/46 | 8.75 III } | 40.96 | } 0 | 0 | + | + | + | | | | 2.5:1 | |
| | | 5.0 I } | | } 0 | 0 | 0 | + | + | | | | 2:1 | |
| | 4/12/46 | 8.75 III | 40.96 | 0 | 0 | + | + | + | | | | 2.5:1 | Blood stream periodically cleared: |
| | 4/17/46 | 10.00 IV | 12.80 | + | + | + | + | + | | | | | |
| | 4/21/46 | 15.00 V | 20.48 | + | + | + | + | + | | | | | |
| | 4/26/46 | 17.50 VI | > 51.20 Θ | 0 | 0 | + | + | + | | | | > 1.5:1 | |
| | 4/29/46 | 17.50 VI | 40.96 | 0 | + | + | + | + | | | | 2.5:1 | Died |
| 3. R.C. | 6/19/46 | 0.31 | 6.40 | 0 | 0 | 0 | 0 | + | + | + | | 2.5:1 | Clinical cure: |
| | 7/8/46 | | ↑ 12.80 | 0 | 0 | 0 | 0 | 0 | + | + | | 2.5:1 | 1 yr. 11 mos. |
| 4. I.K. | 7/30/46 | 0.02 | 0.64 | 0 | + | + | + | + | + | + | | 32:1 | Clinical cure: 1 yr. 10 mos. |
| 5. J.N. | 9/3/46 | 0.156 I | 1.56 | 0 | 0 | 0 | + | + | + | + | | 2:1 | |
| | 9/17/46 | | 0.64 | 0 | 0 | + | + | | | | | 2:1 | |
| | (therapy stopped - 2 positive cultures) | | | | | | | | | | | | |
| | 10/11/46 | 0.156 II | 0.80 | 0 | 0 | 0 | + | + | | | | 1.5:1 | |
| | 10/24/46 | | 0.80 | 0 | 0 | 0 | + | + | | | | 1.5:1 | Clinical cure: |
| | 11/1/46 | | 5.12# | 0 | 0 | 0 | 0 | 0 | 0 | + | + | 1:1 | 1 yr. 8 mos. |
| 6. B.T. | 12/9/46 | 0.02 | 0.16 | 0 | 0 | 0 | + | + | | | | 2:1 | Clinical cure: |
| | | | ↓ 0.08 | 0 | ± | + | + | + | | | | 2:1 | 1 yr. 6 mos. |
| 7. B.P. | 3/25/47 | 0.02 | 1.28 | 0 | 0 | 0 | + | + | | | | 16:1 | Clinical cure: 1 yr. 2 mos. |
| 8. T.M. | 7/18/47 | 0.02 | 6.40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 5:1 | Clinical cure: 10 mos. |
| 9. H.B. | 4/27/48 | 0.04 | 6.40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 2.5:1 | Clinical cure: |
| | 5/1/48 | | ↓ 2.56 | 0 | 0 | 0 | 0 | 0 | 0 | + | + | 2:1 | 2 mos. |
| 10. A.F. | 5/7/48 | 0.04 | 2.56 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 1:1 | Clinical cure: |
| | 5/25/48 | | 2.56 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 1:1 | 1 mo. |

Roman Numerals = Succeeding isolations. 0 = no growth. + = growth.
§ = prophylactic level for oral surgery following discharge. # peak level at 5 minutes. ↑ dose increased. ↓ dose decreased.
Θ = level obtained with concurrent administration of p-amino hippuric acid.

at unnecessarily high concentrations. At these higher levels, complete inhibition of the organism was obtained in all dilutions within the effective range. Pertinent comments on cases of special interest follow; the remainder made uneventful recoveries on dosage schedules shown to be effective by the direct test. Blood cultures taken during therapy were uniformly negative with added Clarase, except where indicated by Roman numerals for later isolations.

Case 1 (Table 1). R. B. This 17-year-old boy had been treated elsewhere on several occasions with the usual empiric type of therapy, each time followed by clinical relapse with isolation of an alpha hemolytic streptococcus from the blood stream. Since levels of 10 Oxford units per ml. proved ineffective when tested against his own organism and positive blood cultures were obtained during therapy, the dose was markedly increased. A concentration of 20 Oxford units was found by direct test to be necessary for complete bacteriostasis. Maintenance of levels above this critical point for protracted periods of time resulted in complete arrest of the infection despite a concurrent attack of appendicitis requiring surgery. Three weeks after discharge a level of 5 Oxford units per ml., obtained during prophylactic therapy for oral surgery, was tested against the initially isolated strain of streptococcus with the predicted result. This case has been fully reported elsewhere[2].

Case 2 (Table 1). H. R. The alpha hemolytic streptococcus strain isolated from blood cultures on this 75 year old male developed *in vivo* resistance to penicillin, probably because treatment, extending over several months, was periodically interrupted, and at times seriously reduced due to lack of penicillin supply. During periods of effective therapy, as established by direct test, repeated blood cultures were sterile. When therapy was inadequate or interrupted, blood cultures became positive again. All strains thus isolated were identical culturally and biochemically, except for the gradual increase in penicillin resistance. The patient died as a result of renal and pulmonary complications following a two-stage prostatectomy. Permission for autopsy was not obtained.

Case 3 (Table 1). R. C. The concentration of penicillin in the blood stream was temporarily increased pending identification of bacterial growth in a single routine blood culture flask. *Staphylococcus albus* was isolated which was judged to be a contaminant. Dosage was reduced to the former level, and recovery was uneventful.

Case 4 (Table 1). I. K. The direct test showed that an unusually high ratio of effective serum level to penicillin sensitivity of the isolated strain (32:1) was necessary for complete bacteriostasis. The penicillin sensitivity of this organism was well within the usual range for this species. Corroborative evidence was obtained from the results of a blood culture drawn simultaneously with blood taken for level, 24 hours after initiation of therapy. Flasks with added Clarase were positive, but those without remained negative. All subsequent cultures were negative and recovery was uneventful.

Case 5 (Table 1). J. N. The first course of penicillin given was too short in duration, and blood cultures were positive within a week following cessation of therapy. The fact that the blood level was adequate, as determined by the direct test, was verified by the satisfactory response to a second full course of therapy (5 wks.) with maintenance of a somewhat lower serum level. Blood cultures were consistently negative for 1 year following discharge as clinically cured.

Several cases of septicemia due to hematogenous spread of organisms from foci of acute and chronic infection are presented in Table 2. *Staphylococcus aureus* infections were mainly selected for further investigation of the efficacy of this type of controlled therapy because of the relatively high initial sensitivity to penicillin of many strains of this species and the tendency for occasional strains to increase progressively in resistance when inadequately treated. In one case (H.W.) a highly resistant alpha hemolytic streptococcus was completely controlled by this method.

Case 1 (Table 2). H. W. Septicemia was probably secondary to chronic foci of infection in the lungs. Blood cultures were negative during the period of adequate therapy as determined by direct test, but became positive when the penicillin concentration was allowed to drop too soon. Re-establishment of the effective level for a longer period permanently sterilized the blood stream. Death occurred from bronchogenic carcinoma with metastasis, without recurrence of the septicemia. At autopsy no evidence of vascular in-

θ = level obtained with concurrent administration of p-amino hippuric

TABLE II.--PENICILLIN THERAPY OF ACUTE AND CHRONIC INFECTIONS WITH HEMATOGENOUS SPREAD

| Case | Etiological Agent | Date | Standard Turbidity Test: Sensitivity in O.u. | Standard Turbidity Test: Serum level in O.u/ml. | Direct Test with Patient's Organism: Serum Dilutions: Undil. | 1:2 | 1:4 | 1:8 | 1:16 | 1:32 | 1:64 | 1:128 | Ratio of Effective Level to Sensitivity | Diagnosis / Outcome of Therapy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. H.W. | alpha hemol. Streptococcus | 1/14/46 | 10.0 I | 12.80 | + | + | + | + | | | | | | Septicemia, |
| | | 1/17/46 | | 40.96 | 0 | + | + | + | | | | | 4:1 | complete arrest; |
| | | 1/19/46 | 10.0 II | 25.60 | + | + | + | + | | | | | | death from other |
| | | 1/23/46 | | 40.96 | 0 | + | + | + | | | | | 4:1 | causes. |
| 2. R.D. (child) | Staphylococcus aureus | 5/17/46 | 0.15 | 3.20 | 0 | 0 | 0 | 0 | 0 | + | + | | 1.5:1 | Septicemia Osteomyelitis: disch. as cured |
| 3. M.R. (child) | Staphylococcus aureus | 11/16/46 | 0.15 | 0.08 | + | + | + | (empiric therapy) | | | | | | Septicemia Osteomyelitis: |
| | | 11/18/46 | | ↗ 3.20 | 0 | + | + | + | + | | | | 21:1 | disch. as cured |
| 4. D.K. | Staphylococcus aureus | 1/5/47 | 0.31 I | 20.00 | 0 | 0 | 0 | 0 | + | | | | 8:1 | Septicemia Prostatitis |
| | (2nd adm.) | 10/22/47 | 1.25 II | (0.625 u. streptomycin) | | | | | | | | | | |
| | | | | § - | 0 | 0 | 0 | 0 | 0 | 0 | + | + | | |
| | | 10/27/47 | | § - | 0 | 0 | 0 | 0 | 0 | 0 | + | + | | disch. as cured |
| 5. R.W. | Staphylococcus aureus | 10/1/47 | .625 | 1.28 | 0 | + | + | + | | | | | 2:1 | Septicemia, |
| | | 10/2/47 | | 1.28 | 0 | + | + | + | | | | | 2:1 | chronic |
| | | 10/9/47 | | •• 1.28 | 0 | + | + | + | | | | | 2:1 | osteomyelitis: |
| | | 10/9/47 | | •• 2.56 | 0 | 0 | + | + | | | | | 2:1 | Septicemia |
| | | 10/13/47 | | 1.28 | + | + | + | + | | | | | | cured, disch. |
| | | 10/17/47 | | ↗ 3.20 | 0 | 0 | + | + | | | | | 2.5:1 | |
| | (2nd adm.) | 1/7/48 | .625♯ | 3.20 | 0 | 0 | + | + | | | | | 2.5:1 | Draining sinus |
| 6. L.R. (baby) | Staphylococcus aureus | 12/3/47 | .31 I | (Empiric therapy) | | | | | | | | | | Septicemia |
| | | 12/8/47 | .625 II | 0.80 | qns | + | + | | | | | | | Pulmonary abscess |
| | | 12/10/47 | | ↗ 5.12 | 0 | 0 | 0 | 0 | + | + | | | 1:1 | Osteomyelitis: disch. as cured |
| 7. Baby R (Premature) | Staphylococcus aureus | 1/11/48 | 2.5 I | (0.625 u. streptomycin) | | | | | | | | | | Meningitis |
| | | 1/14/48 | | § - | 0 | 0 | 0 | 0 | 0 | 0 | + | + | | Septicemia |
| | | 1/27/48 | 2.5 II | (> 80 u. streptomycin) | | | | | | | | | | Osteomyelitis |
| | | 2/5/48 | 2.5 II | 6.40 | 0 | 0 | + | + | + | | | | 1.5:1 | died |

§ Penicillin and Streptomycin (See case discussions)
•• Romansky formula, 8 & 12 hrs. respectively
↗ Dose increased
♯ Strain from sinus; blood cultures negative
0 = no growth
+ = growth

fection could be found, so presumably the intensive therapy had been effective.

Cases 2 and 3 (Table 2). Of notable interest is the marked difference in ratio of effective serum penicillin concentration during therapy to the sensitivity of the strains of *Staphylococcus aureus* isolated from blood cultures of these two otherwise essentially similar cases (1.5:1 and 20:1, respectively). In Case 3 (M. R.) septicemia developed during empiric therapy, which was shown by the direct test to be inadequate. Sharply increasing the dosage to serum levels completely bacteriostatic for the isolated strain resulted in complete recovery. Both patients were discharged as cured.

Case 4 (Table 2). D. K. Acute septicemia and meningitis developed following a partial prostatectomy in this 65 year old male. Subsequent penicillin dosage was shown to be more than adequate by the direct test. Blood and spinal fluid cultures became negative, and therapy was stopped. Intermittent low grade chronic septicemia subsequently developed, and the patient was treated with small empiric doses of penicillin alternated with sulfonamide drugs both in the hospital and at home without complete eradication of the infection. Some months later he was readmitted for study. Apparently the same strain of hemolytic *Staphylococcus aureus* was again cultured from peripheral blood, but its resistance to penicillin had increased 4-fold. Since the organism was sensitive to streptomycin, combined therapy was instituted, and the antibiotic level of the blood serum was demonstrated to be adequate to control the infection. Therapy was continued for a longer period, and the patient discharged with no further recurrence of the septicemia.

Case 5 (Table 2). R. W. Septicemia developed secondary to chronic osteomyelitis, with a draining sinus. Penicillin levels demonstrated to be adequate for control were maintained until complete control of the infection was obtained. Prophylactic levels during a later admission for surgery to the sinus were satisfactory when tested against a similar strain of *Staphylococcus aureus* isolated from the drainage. Recovery was satisfactory without recurrence of the septicemia, and the patient discharged.

Case 6 (Table 2). L. R. This 3 weeks old baby was admitted for cellulitis of the finger and possible pneumonitis. *Staphylococcus aureus* was isolated from the excised finger and blood stream. Empiric therapy based on age and weight was instituted. A second blood culture drawn during therapy was again positive for *Staphylococcus aureus*, but its sensitivity to penicillin had decreased. The patient's serum had 4 + growth in 1:2 dilution (undiluted serum, quantity insufficient) and the dosage was increased immediately. In the meantime a lung abscess and several foci of acute osteomyelitis had developed. A second test at the new dosage schedule established that therapy was more than adequate for control of the organism, and it was maintained at this level for 3 weeks. Subsequent blood cultures were sterile, and gradual resolution of all foci of infection, without surgical intervention, took place. In an attempt to hasten resolution and prevent possible secondary invaders from the lung abscess, streptomycin was given later in addition to pencillin. All roentgenograms were normal at time of discharge and follow-up blood cultures negative.

Case 7 (Table 2). Baby R. This one day old premature infant was admitted to the hospital following home delivery without medical attention with a cord stump infection and meningitis symptoms. *Staphylococcus aureus* was cultured from the umbilicus, spinal fluid and peripheral blood. Pending identification of the isolated bacteria, both penicillin and streptomycin were given. Both drugs were continued because of the relatively high resistance to penicillin *in vitro*. The combined antibiotic blood serum level was more than adequate for control when tested directly and the spinal fluid and blood stream rapidly became sterile. Therapy was discontinued, evidently too soon. Multiple foci of acute osteomyelitis developed, and the blood culture became positive once more. Sensitivity to penicillin was unchanged, but the organism was now resistant to 80 micrograms of streptomycin. Penicillin therapy was resumed with blood serum levels shown by the direct test to be adequate for control of the infection, providing good penetration into infected areas could be obtained. Unfortunately, other foci appeared throughout the body. A week later knee aspiration cultures yielded a third isolation of *Staphylococcus aureus*. Penicillin sensitivity remained the same (2.5 Oxford units) and sensitivity to streptomycin had apparently decreased to 10 micrograms since withdrawal of this antibiotic. Despite continued therapy the clinical course became progressively worse, and the patient died. Undoubtedly, prematurity and debilitation as well as insufficiently prolonged treatment in the early stages were contributory factors in the failure of therapy in this infant.

**Comment:** In spite of one frank failure, in our opinion there is definite value in using this type of planned therapy, especially in cases of staphylo-

# Strain from sinus; blood cultures negative
0 = no growth
+ = growth

coccic osteomyelitis in children. Antibiotic therapy in no way obviates the necessity for indicated surgical procedures, particularly where sequestra have formed and in relatively avascular foci. During the early acute stage of osteomyelitis, antibiotic therapy has proven effective as the only adequate therapeutic measure, assuming that blood serum concentrations demonstrated to be adequate for complete bacteriostasis of the patient's own organism are maintained for sufficient periods of time. In our opinion sterile blood cultures are not, *per se*, adequate criteria for cessation of therapy.

Our procedure is not routinely used for relatively sensitive organisms found in transient bacteremias and acute infections where the effectiveness of therapy is readily evidenced by the clinical response of the patient. As a control, however, in further study of the relationship between effective penicillin serum concentrations and *in vitro* sensitivity, several such cases were investigated (Table 3, *Group* A). All were acute septicemias treated with penicillin following isolation of a sensitive organism from peripheral blood. Although variations in the ratio of effective serum level to sensitivity were noted, the range was less marked. All infections promptly subsided following therapy, and repeat blood cultures were negative before discharge.

The last 3 cases (Table 3, Group B) further illustrate the utility of this method for controlling therapy in the treatment of resistant organisms, or mixed infections, especially when the use of more than one antibiotic is indicated. Immediate direct test of the bacteriostatic property of both spinal fluid and blood serum during various types of combined therapy has proven very valuable, pending results of individual sensitivity tests with subsequent elimination of non-contributory drugs.

There are two cardinal principles in the effective treatment of subacute bacterial endocarditis and similar septic conditions with penicillin; namely, the amount and the duration of therapy. The latter is beyond the scope of this report, except in so far as optimal therapy may be expected to shorten the duration. In general it has been our experience that 4 to 5 weeks are usually necessary to insure complete, permanent arrest, but no objective criteria have yet been found.

The amount of penicillin to be given will depend upon the minimum blood serum concentration desired. The effective blood level appears to us to be the resultant of 3 sets of variable factors. First, and subject to a certain degree of control, are route of administration, vehicle employed, number of units and interval of each injection, and the use of artificial kidney blocks. A second group, subject to a greater degree of variability, is inherent in the individual patient: rate of absorption, rate of excretion and status of kidney function, inactivation by binding with plasma proteins,[4] and specific antibody production. A third group concerns properties inherent in the individual bacterium such as growth requirements, metabolism, and reaction to antibiotics. In addition to the *in vitro* sensitivity as usually defined, is the unpredictable variation observed in the concentrations of assayable penicillin which must be achieved in patients' sera in order to obtain the same degree of bacteriostasis. Eagle[1] in his excellent discussion of the therapeutic significance of blood penicillin levels, calls attention to two additional factors of possible significance in this respect. Concentrations of penicillin slightly above the minimal bacteriostatic level appear to increase the *rate* of death of the susceptible organism; greatly increased concentrations, on the other hand, paradoxically appear

TABLE III.--ANTIBIOTIC THERAPY IN ACUTE SEPTICEMIA DUE TO VARIOUS SPECIES OF PATHOGENIC BACTERIA

| Case | Etiological Agent | Date | Standard Turbidity Test: Sensitivity in O.u. | Standard Turbidity Test: Serum level in O.u./ml. | Direct Test with Patient's Organism: Serum Dilutions: Undil. | 1:2 | 1:4 | 1:8 | 1:16 | 1:32 | 1:64 | 1:128 | Ratio of Effective Level to Sensitivity | Diagnosis / Outcome of Therapy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group A Penicillin Therapy | | | | | | | | | | | | | | |
| 1. S.K. | Staphylococcus aureus | 1/4/47 | 2.5 | 20.48 | 0 | 0 | 0 | 0 | + | + | + | + | 1:1 | Bacteremia<br>Recovered |
| 2. D.E. (child) | Pneumococcus Type 18 | | .0025 I<br>.31 I\ | Treated empirically: no level taken | | | | | | | | | | Bacteremia<br>Pneumonia |
| | Staphylococcus albus | 6/4/47 | .31 II | ↗ 10.24 | 0 | 0 | 0 | 0 | 0 | + | + | + | 2:1 | Recovered |
| 3. A.L. | "minute" hemol. Streptococcus | 10/7/47 | .04 | .64 | 0 | 0 | 0 | 0 | 0 | + | + | + | 1:1 | Septicemia<br>Acute Rheu. Arthritis<br>Recovered |
| 4. M.S. | beta hemol. Streptococcus | 3/10/48 | .02 | 2.56 | 0 | 0 | 0 | 0 | 0 | + | + | + | 8:1 | Septicemia<br>Thrombophlebitis<br>Recovered |
| Group B Combined Therapy | | | | | | | | | | | | | | |
| 1. N.B. (child) | Staphylococcus aureus | 10/14/47 | .15 | (.625 u. streptomycin) Spinal fluid | 0 | 0 | 0 | 0 | 0 | 0 | + | + | | Brain abscess outside pt. not followed |
| 2. T.N. (child) | Staphylococcus aureus | 3/27/47 | 5.0 | (.625 u. Streptomycin) blood serum | 0 | 0 | 0 | 0 | 0 | + | + | + | | Septicemia. Extensive burns. Sept. controlled. Death due to burns |
| 3. L.G. (child) | Hemophilus influenzae | 4/20/48 | 1.25 | (2.5 u. Streptomycin) spinal fluid | 0 | 0 | 0 | 0 | 0 | + | + | + | | Meningitis<br>Recovered |

0 = No growth
\+ = Growth
↗ = Dosage increased

to decrease the death rate of certain strains of streptococci.

Many, if not all, of these variables are susceptible to individual evaluation, but the methods are both time consuming and tedious. Assay of the effective blood serum penicillin concentration by using the organism isolated from the patient under treatment offers a direct, rapid and relatively accurate means of evaluating adequacy of therapy. By this method the minimal effective level is that concentration of assayable blood serum penicillin which can be shown to be completely bacteriostatic for the strain isolated. We believe the optimal therapeutic level should be at least twice the minimal effective level, as shown by our direct test. Penicillin dosage schedules should be adjusted to maintain the necessary blood serum concentration for extended periods of time.

**Summary and Conclusions.** 1. A direct test for determining the therapeutic value of penicillin levels by assay with the strain of bacteria isolated from the patient under treatment is described.

2. Minimal and optimal effective blood serum penicillin concentrations applicable to therapy of subacute bacterial endocarditis and infections due to relatively resistant strains of bacteria are defined.

3. It is recommended that penicillin therapy in such cases be based on maintenance of adequate serum levels as judged by the direct test for considerable periods of time.

4. It is further recommended that unnecessarily high levels are not only economically wasteful, but may possibly result in prolonging the duration of therapy by reducing the bactericidal rate of the strain involved.

5. Evidence is presented to prove that this type of planned therapy is a valid and effective basis for treatment of subacute bacterial endocarditis and chronic infections due to relatively resistant strains of susceptible organisms.

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# PERICARDIAL EFFUSION: A CONSTANT, EARLY AND MAJOR FACTOR IN THE CARDIAC SYNDROME OF HYPOTHYROIDISM (MYXEDEMA HEART)*

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Since Zondek's[31] first report in 1918, it has been recognized that a certain number of patients with myxedema develop cardiac phenomena that have been designated "myxedema heart." These include: (1) a great increase in the size of the cardiac dulness on percussion, and of the cardiac shadow on fluoroscopy and in the roentgenogram; (2) faintness of the heart sounds on auscultation; (3) diminished minute volume of cardiac output; (4) feeble cardiac pulsations as seen fluoroscopically; (5) reduced voltage in the electrocardiogram, especially of T-waves that are flattened or even inverted and at times a shortened Q-T interval; and (6) complete reversibility of these changes to normal under treatment with thyroid hormone.

These phenomena have usually been attributed by clinicians to a uniform dilatation, cryptic in nature, of all cardiac chambers. The electrocardiographic changes, as Bellet and McMillan[1] state, have been explained by alterations in the myocardium and by easier dissipation of the cardiac action current through myxedematous tissue. Pathologists have little to say on the subject: as Boyd[3] points out, the lack of autopsy material is responsible for our dearth of accurate knowledge. Boyd's own experience includes no necropsy and only 1 patient studied by Roentgen-ray.

An occasional roentgenologist has commented on the similarity of the roentgenologic phenomena in these cases to those of pericardial effusion. Thus, Ungerleider and Gubner[28] suggest that when *marked* enlargement is present, pericardial effusion should be suspected. They point out that an effusion could largely or entirely explain such findings as the increased size of the cardiac shadow, the diminished amplitude of the cardiac pulsations, the faint heart sounds and even the electrocardiographic changes.

Yet there are on record comparatively few instances of the proved presence of pericardial effusion in patients with myxedema. Gordon[12] in 1929 reported the first case and in 1935 discussed the subject before the Associ-

* Read in abstract before the Association of American Physicians in Atlantic City, N. J., on May 4, 1948.

ation of American Physicians.[13] Since then, an additional 16 publications bring to 21 the total number of recorded cases, 16 proved during life by pericardial tap and 5 found at necropsy. Only Scherf[25] has observed as many as 3 cases, and ventures the belief that pericardial effusion is often present "in the *large* hearts of myxedema". Harrell and Johnston[14] report 2 patients with positive taps. Lerman, Clark and Means[19] cite post-mortem records in which 2 of 5 myxedema cases were found to have pericardial effusions. All the others[2,4,5,8,9,10,15,17,18,20,21,23,29] are single case reports, sometimes one of a number (up to 20) of cases of myxedema heart studied by these authors. Without exception, the cases with proved effusion were those in which a very large cardiac size or shadow gave the clue to effusion and suggested a diagnostic tap.

The prevailing clinical view, therefore, is that pericardial effusion is only rarely a contributory factor to the enlargement of the cardiac silhouette in this disease.[30] In a group of 4 consecutive cases of myxedema we have made observations which we think warrant a revision of this view.

**Case Reports.** CASE NO. 1. Mrs. S. M., a white woman, aged 61 years was admitted to this hospital on Jan. 30, 1947, with a chief complaint of a swollen face and easy fatigability. In 1935, because of thyrotoxicosis, she had been subjected in this hospital to a thyroidectomy. At that time the heart was of normal size. (Fig. 1a).* Several months later she noticed that she tired easily, was short of breath on exertion, was constipated and began to gain weight. The presence of myxedema was recognized and thyroid treatment instituted with good results. During the succeeding years she was observed from time to time in the Out-Patient Department and did well or not so well, depending on her observance of treatment. For some weeks prior to the present admission she had taken no thyroid.

*Physical examination* showed an obese (168½ pounds, height 62 inches) elderly woman with the typical heavy facies of myxedema. The skin was dry and the hair dry and brittle. The cardiac dulness was greatly enlarged, the apex beat not visible; the sounds were faint and there was a soft systolic murmur. The blood pressure was 138/90 and the pulse 80 to 90. Although she had dyspnea on exertion, there were no objective signs of cardiac failure: the lung bases showed no rales, the liver was not enlarged and there was no edema of the feet or ankles.

*Laboratory data:* Basal metabolic rate—18%, blood cholesterol 680 mg. per 100 cc., serum protein 7.5 gm., serum albumin 4.7 gm., serum globulin 2.8 gm., A/G ratio 1.7; inorganic phosphorus 3.4 mg., alkaline phosphatase 2.4 units; blood count: erythrocytes 4,700,000, hemoglobin 12 gm., leukocytes 6800 (neutrophils 53%, lymphocytes 37%, monocytes 2%, eosinophils 5%, basophils 3%); urine analysis: Sp.gr. 1020, albumin 1+, other findings normal.

The electrocardiogram (Fig. 5A) showed somewhat reduced voltage of the complexes, a P-R interval of 0.18 second, and negative T-waves in the limb leads and in CR4 and CR5: "findings compatible with hypothyroidism".

A routine chest film (Fig. 1b) showed a huge heart shadow, and by fluoroscope the cardiac pulsations were seen to be sluggish and small. The roentgenologist made a diagnosis of cardiac dilatation.

However, the faintness of the heart sounds and lack of an apex impulse suggested to one of us (L.A.S.) the presence of a pericardial effusion. A pericardial puncture yielded 310 cc. of a straw-colored fluid which was replaced with an equal amount of air. Now the roentgenogram (Fig. 1c) showed a heart comparable in size to that of 12 years before, within a greatly distended pericardium that still contained much fluid. The pericardial sac had a thin wall that certainly was not edematous. Under the fluoroscope the normal-sized heart showed hyperactive pulsations within the pneumo-hydro-pericardium, quite different from the feeble pulsations of the silhouette seen before tapping.

*Course:* Treatment with thyroid substance was then begun, with good results. On Feb. 25, 1947, 26 days after admission, her metabolic rate was +4% and the cholesterol 258 mg. At the same time the cardiac outline diminished markedly, with disappearance of the pericardial effusion (Fig. 1d). There was also a return toward the normal in the electrocardiogram (Fig. 5B).

We have observed this patient in two additional periods of hypothyroidism, induced with her consent by omitting treatment. In

* All chest roentgenograms here used are 4 foot films, not teleoroentgenograms.

January, 1948, when she had been without medication for several weeks, she had gained 20 pounds, her cardiac dulness was enlarged and the heart sounds were feeble. The roentgenogram showed again an increased cardiac shadow. Paracentesis again showed the presence of a straw-colored effusion in the pericardial sac. Under thyroid treatment there was again return to normal in the several findings. In a second period of low metabolism 2 months later there was clinical and roentgenological evidence of pericardial effusion, but we did not feel justified in doing another tap.

She is now being kept in a euthyroid state and has no apparent cardiac abnormality.

These observations led us to think promptly of the possibility of pericardial effusion in the next patient with myxedema whom we encountered.

Case No. 2. Mrs. J.M., a white woman aged 67, was seen in 1947 because of chief complaints of dizziness, lassitude and intolerance of cold. In 1923 she had a partial thyroidectomy because of thyrotoxicosis that had involved a weight loss of 106 pounds. In 1935

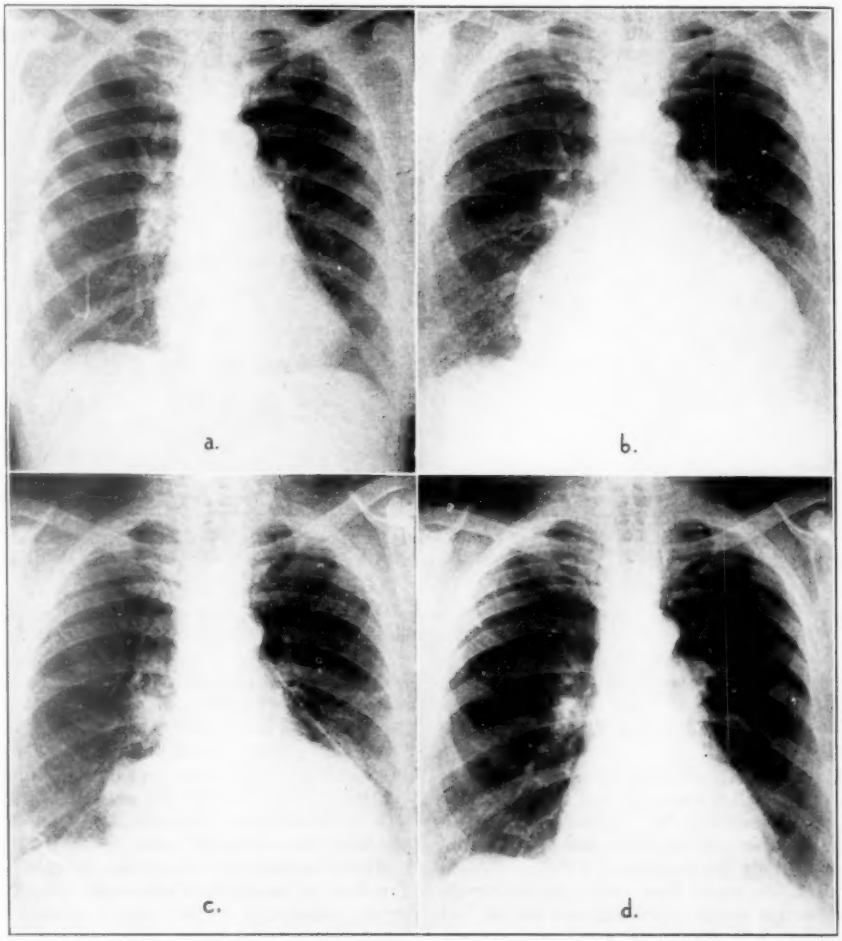


FIG. 1.—Case 1: "Cardiac" silhouettes in myxedema. (a) Routine chest film in 1935 when patient, then aged 49, had thyrotoxicosis, (b) January, 1947; patient myxedematous. Roentgenologic diagnosis: "cardiac dilatation". But pericardial tap yielded 310 cc. of fluid which was replaced (c) with air. Note thin line of pericardium, not edematous. (d) Three weeks later, after thyroid medication, "heart size within normal limits".

there were renewed evidences of thyrotoxicosis for which she received irradiation of the thyroid, with resultant improvement. In 1943 the myxedema began that brought her to us 4 years later.

*Physical examination* showed a short fat woman (61 inches, 161 pounds) in no distress. The face was puffy and the hair dry. The cardiac dulness was greatly enlarged, the heart sounds were feeble, and there was a soft mitral systolic murmur. There was no evidence of circulatory failure: no basal rales, hepatic swelling or peripheral edema. The blood pressure was 96/56 and the pulse rate 86.

*Laboratory data:* Basal metabolic rate—25%, serum cholesterol 420 mg. per 100 cc.: blood count: 3,900,000 erythrocytes, 12.6 gm. hemoglobin, 4800 leukocytes; urine findings within normal limits.

CASE 3: Mrs. V.H., a white woman of 58 years, was admitted in June, 1947, because of post operative myxedema. In 1940 she had had a subtotal thyroidectomy for thyrotoxicosis, and in the years that followed she gained 60 pounds in weight.

*Physical examination* showed an obese subject (198 pounds, 64¼ inches) with no other positive findings. The blood pressure was 130/80, the pulse 72. The precordial dulness was not much enlarged, but the heart sounds were of fair quality. There were neither signs nor symptoms of any cardiac failure.

*Laboratory studies:* A basal metabolic rate of —18%, serum cholesterol 608 mg. per 100 cc., normal blood count and urine findings, a normal sugar tolerance curve.

The electrocardiogram showed upright P-waves, P-R interval 0.14 second, low voltage in all leads, T-waves low in all leads.

FIG. 2.—Case 2: (a) Chest film after removal of 150 cc. of pericardial fluid and replacement with air in myxedematous patient. (b) Diminished heart size after 6 weeks of thyroid medication.

Under the fluoroscope the large heart size was confirmed.

The electrocardiogram showed low voltage in all leads, P-waves upright in all leads, P-R interval 0.16 second, QRS not remarkable, T-waves diphasic in Leads I and II and in the precordial leads.

Pericardial tap yielded 150 cc. of straw-colored fluid that was replaced with air. The roentgenogram (Fig. 2a) showed the presence of considerable residual fluid and again a thin non-edematous pericardium.

*Course.* Six weeks later under thyroid treatment she was much improved: her weight had dropped to 147, the basal metabolic rate was —10%, the serum cholesterol 240 mg. The electrocardiogram showed increased voltage of the complexes and upright T-waves, and the roentgenogram showed a definite decrease in the heart size (Fig. 2b).

The roentgenogram (Fig. 3a) was reported as showing the heart to be "moderately but definitely enlarged, with nothing characteristic in the configuration. The enlargement is apparently both right and left sided. We understand that pericardial effusion is considered from the clinical standpoint, but from the Roentgen standpoint we feel unable either to confirm or rule out this impression."

A pericardial tap nevertheless yielded 150 cc. of a straw-colored fluid.

Three weeks later, under thyroid treatment, she had a basal metabolic rate of —3%, a serum cholesterol of 350 mg., a normal electrocardiogram and a normal-sized heart shadow (Fig. 3b).

CASE 4: Mrs. M.S., a white woman aged 62 years, was admitted to hospital on February 16, 1948, because of failing vision due to cataracts. For 7 years she had been gaining

weight, was easily fatigued and lost a good deal of hair. She had also had definite anginal symptoms, with precordial pain radiating to the neck and left arm upon exertion.

*Physical examination* showed, in addition to obesity and cataracts, an enlarged cardiac dulness with feeble heart sounds, a soft systolic mitral murmur and no palpable cardiac impulse. The blood pressure was 120/74 and the pulse 86.

*Laboratory data:* A basal metabolic rate of —42%, serum cholesterol 37.0 mg. per 100 cc.; blood count: 3,400,000 erythrocytes, 9.9 gm. hemoglobin, 4900 leukocytes with a normal differential count; urine: a trace of albumin; serum protein 6.4 gm., serum albumin 4.0 gm., globulin 2.4 gm., calcium 10.6 mg.

The electrocardiogram showed low voltage, upright P-waves, P-R interval 0.16 second, flat T-waves and QRS changes suggesting coronary insufficiency.

The roentgenogram showed an enlarged heart shadow, and the roentgenologist spoke

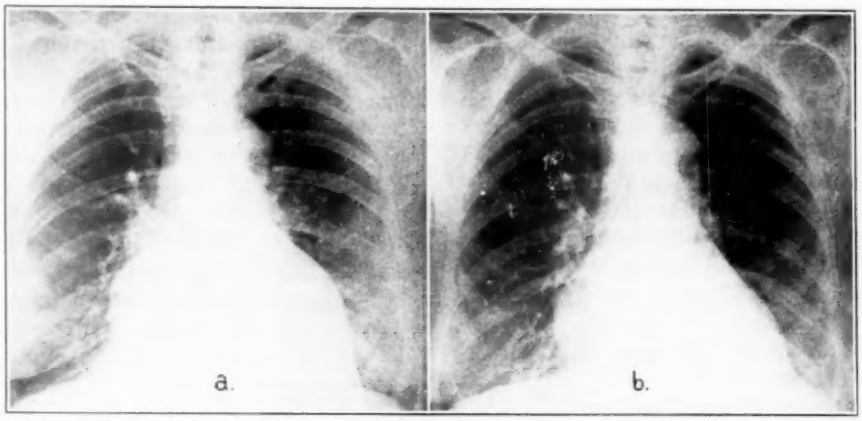


FIG. 3.—Case 3: (a) Chest film of myxedematous patient; cardiac shadow does not suggest presence of pericardial effusion; yet tap yielded 150 cc. of fluid. (b) Three weeks later, under thyroid medication, normal heart shadow.

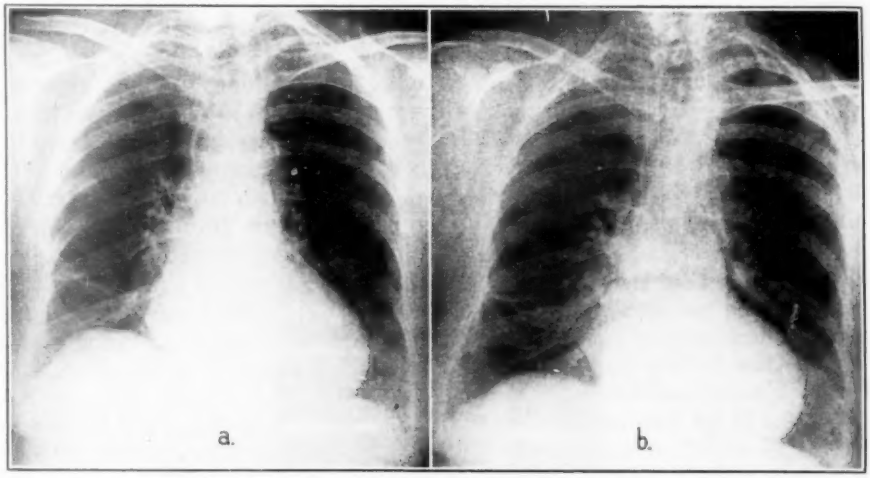


FIG. 4.—Case 4: (a) Chest film of myxedematous patient; roentgenologic diagnosis: "enlarged heart shadow, especially left ventricle, no pericardial effusion". But tap yielded 105 cc. of fluid, which was replaced (b) with air. Note thin line of pericardium.

of a large left ventricle and an "aortic configuration", but made no mention of possible pericardial effusion (Fig. 4a).

Since the clinical diagnosis of spontaneous or primary myxedema was established, it was decided to perform a pericardial paracentesis. The tap yielded 105 cc. of straw-colored fluid like that of the other 3 cases. The fluid was replaced with an equal amount of air and another film made (Fig. 4b) that again made visible the thin-walled pericardium.

silhouette definitely diminished in size. A cataract extraction was performed without mishap.

Here, then, are 4 consecutive cases of myxedema in each of which the presence of a considerable pericardial effusion was proved. Yet none had any evidence of congestive heart failure and 2 of the 4 had relatively little

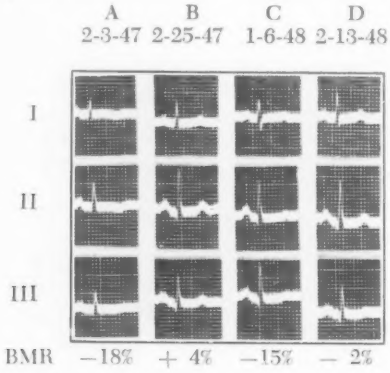


FIG. 5.—Electrocardiographic findings in Case 1 during (A, C) 2 periods of low metabolism (pericardial effusion proved by tap in each period) and (B, D) 2 periods of normal metabolism after thyroid medication. Note T wave changes and low voltage in (A) and (C), and improvement in these points in (B) and (D).

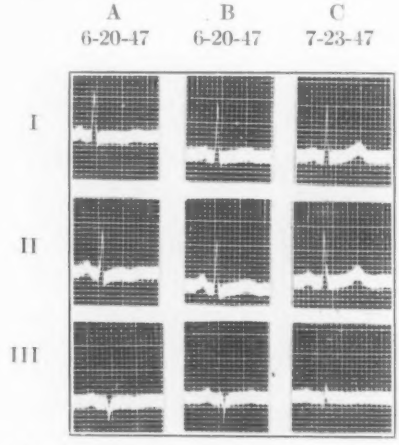


FIG. 6.—Improvement in electrocardiogram observed in Case 3 as shown by records made on same day, (A) before and (B) after the removal of 150 cc. of pericardial fluid. Further improvement shown in (C) after 33 days of thyroid medication.

Thyroid treatment was cautiously given to this patient because of the history of angina. On 30 mg. of thyroid daily her metabolic rate remained at −26%, although the cholesterol fell to 176 mg. Nevertheless the electrocardiogram showed increased voltage and T-waves that were more nearly upright and the cardiac

enlargement of the heart shadow. In each the exhibition of thyroid resulted in a regression of the effusion. In other words, the effusion played both a constant and a considerable role in the cardiac findings and was related

directly to the myxedema. In Case 1 this relationship was demonstrated 3 times.

We also believe that the *electrocardiographic changes* noted in myxedema heart by many observers may largely, if not wholly, be caused by the fluid in the pericardial sac. The degree of change under treatment has suggested to others that absorption of fluid seemed at least partly responsible for the improvement noted in the tracings. Moreover the ability to reproduce these changes makes the effusion a more likely explanation than purely myocardial changes. Figure 5 shows two such observations in our Case 1. Nevertheless, myocardial edema might still be present together with the effusion and so could be responsible for some of the changes before, as compared with after treatment.

Therefore, we call particular attention to this observation on Case 3: the improvement in electrocardiograms made on the same day, just before and just after the removal of 150 cc. of pericardial effusion (Fig. 6). This degree of change would occur only after at least 10 days of thyroid administration. Moreover, it is clear, on study of the films of the other 3 cases that some fluid must have remained in this case too, the removal of which would have effected an even closer approach to the final normal tracing at the end of thyroid treatment. (This type of electrocardiographic study could not be made in the other 3 cases because in them we were anxious to get contrast pictures of pericardium and fluid by means of air replacing the fluid.)

That fluid could be the main cause of the electrocardiographic changes also has experimental support. Katz, Feil and Scott[16] injected salt solution into the pericardial sac of dogs and found resultant changes in the electrocardiogram, including smaller Q-R-S complexes and at times a shortened S-T segment. Scherf[24] in similar experiments noted that the voltage of recorded waves was reduced by one-half, but returned promptly to normal when the fluid was withdrawn from the pericardium.

Further evidence in favor of the major role of pericardial effusion in "myxedema heart" is furnished by the records of the cases reported by others. Of the 16 patients that were observed clinically, 3 were known to have had their effusions during 4, 5 and 16 years respectively[2,9,20] before the myxedema was recognized; yet all 3 did well under thyroid treatment and were free of cardiac difficulties for one or more years at the time of reporting. Boivin's patient[2] had at least 75 pericardial taps before she received thyroid medication at the age of 64. It is hard to believe that these patients could have had severe myocardial disease or much cardiac dilatation for so long a time and yet do so well under treatment.

Effusions into the serous cavities, including the pericardium, have been observed in experimental myxedema by Tatum[26] in rabbits and by Goldberg[11] in sheep.

Furthermore, there are several good reasons against the view that myocardial disease and cardiac dilatation play the chief role in "myxedema heart":

1. Congestive failure is relatively rare in myxedema, as pointed out by Means.[22] What is more, it is uncommon even in the reported patients with obvious "myxedema heart". This has been well discussed by Waring,[29] who points out that in "myxedema heart" the picture is "adynamic", with lethargy, slow pulse and respirations, sluggish heart action; perhaps dyspnea on exertion, but rarely orthopnea; with infrequent cyanosis, pulmonary or hepatic congestion and with normal venous pressure. In congestive failure, on the other hand, the picture is

"dynamic", with tachycardia, dyspnea, pulmonary and hepatic congestion, increased venous pressure and dependant edema.

2. Pericardial effusion in myxedema does not of itself embarrass the cardiac function to any notable degree. This is due probably to two reasons: the slow development of the effusion and the rather surprising distensibility of the pericardium. These account for the relative lack of any tamponade effect, although in each of our patients the pulse rate was slower 24 hours after tapping (80, 72, 70 and 60 respectively) than it had been before (96, 90, 86, and 80). They also account for the large quantity of effusion that may accumulate without much clinical reaction: in Howard's case[15] at necropsy a normal-sized heart was found in an unsuspected effusion measuring 4000 cc.

3. The blood volume is increased in congestive failure. In myxedema the blood volume is usually decreased. It was diminished in the 3 of our patients so studied.

4. The Q-T interval (electric systole), as Tung[27] has pointed out, is increased in cardiac enlargement without effusion; it is normal or diminished in pericardial effusion. It was normal or diminished in our 4 patients.

Nature of the Pericardial Effusion. In each of our patients the pericardial punctate had a fairly similar composition. While detailed analyses will be published elsewhere, these salient points are here noted: Each fluid was straw-colored and nearly clear. The specific gravities ranged from 1012 to 1025. The electrolytes (sodium, potassium) were present in about the same concentrations as in the blood. Cholesterol was present in the fluids, but in not over 20% of the amounts observed in the blood (e.g., Case 1: serum cholesterol 680 mg. per 100 cc., punctate 136 mg.; Case 2: serum 608 mg., punctate 76 mg.; Case 3: serum 460 mg., punctate 90 mg.). The total protein figures for punctates were also somewhat lower than for the blood (e.g., Case 1: Serum total protein 7.5 gm., albumin 4.7 gm., globulin 2.8 gm.; punctate total protein 5.9 gm., albumin 4.4 gm., globulin 1.5 gm.). The globulin fraction was relatively lower in punctate than in serum, the extreme figures being in Case 4: serum protein 6.4 gm., albumin 4.0 gm., globulin 2.4 gm., punctate protein 2.8 gm., albumin 2.5 gm., globulin 0.3 gm.

The cellular elements were leukocytes that in total numbers ranged as high as 488 per c. mm., of which 23% were neutrophils and 77% lymphocytes. There were no erythrocytes. The fluids were all sterile on culture, including special studies for tubercle bacilli.

Mechanism of Pericardial Effusion in Myxedema. We have no explanation for the occurrence of the effusion into the pericardium or the other serous cavities. We wish, however, to endorse the view of Means and his colleagues[19] that "Myxedema heart" is not a disease of the heart but a manifestation of the disease myxedema. Myxedema heart, and especially massive pericardial effusion which we believe is its major component, appears to be a function of virtual athyrosis, for the fluid clears up on thyroid medication before the metabolic rate has returned to normal. This is a fortunate circumstance, for thyroid medication in myxedema must be used cautiously in all cases. As Christian[7] and others have pointed out, the uncontrolled use of such treatment may have serious and even fatal consequences. Especially in the presence of anginal symptoms is such caution necessary, but even they do not flatly contraindicate treatment, since angina in the myxedematous is at times even helped by thyroid medication.

THE DIAGNOSIS OF PERICARDIAL EFFUSION. Our observations emphasize the fallibility of the roentgenological method in the diagnosis of pericardial effusions, even when they are of considerable size. A glance at the illustrations for our cases will show the uselessness of a sign that continues to be mentioned both in roentgenological and physical diagnosis as indicative of effusion: the obliteration of the acute reentering cardio-hepatic angle. Much more significant are the feeble sluggish movements of the shadow on fluoroscopy, the diminished heart sounds and the obliterated or feeble apex impulse with a widened precordial dulness on physical examination and possibly the added help from the electrocardiogram. Perhaps the roentgenologist should acknowledge his limitations by speaking of the "pericardial" rather than the "cardiac" silhouette.

**Summary and Conclusions.** 1. "Myxedema heart" is of not uncommon occurrence in untreated myxedema and has heretofore been explained on the basis of a uniform dilatation of all cardiac chambers. Little consideration has been given to pericardial effusion, a condition reported to date in only 21 cases of myxedema.

2. Yet in 4 consecutive patients with myxedema we have demonstrated considerable pericardial effusion, even when roentgenologic findings were not suggestive of its presence, and in the absence of any evidence of congestive failure.

3. In all 4 patients the effusion cleared up under thyroid medication, and in one patient this phenomenon was observed in 2 additional periods of hypothyroidism induced with the patient's consent by omitting treatment.

4. The electrocardiographic picture of "myxedema heart", hitherto ascribed to myocardial changes and to the effects of tissue edema, can even better be explained by the effect of a blanketing pericardial effusion. This view is not only suggested by the previous experimental evidence of others, but is strongly supported by our findings of marked electrocardiographic improvement between 2 tracings taken on the same day just before and just after the aspiration of the pericardial effusion.

5. We therefore believe that pericardial effusion is a constant, an early, and the major factor in the cardiac findings in myxedema ("myxedema heart").

6. "Myxedema heart" is not a cardiac disease, but a manifestation of the disease myxedema, and has the much more favorable therapeutic and prognostic outlook of the latter.

7. The nature of the pericardial effusion is described.

8. The diagnostic criteria of pericardial effusion and the limitations of its roentgenologic recognition are briefly discussed.

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# SOME CARDIOLOGICAL PROBLEMS OF THE TROPICS

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In the 1930-1931 Report of the former "Junta de Caridad de San José", Rotter[30] gives a frequency of 6% of affections of the circulatory system as cause of death among 559 autopsies carried on at this hospital. We have now analyzed 8000 autopsies as a basis for this study, finding a cardiovascular mortality of 768 cases (9.6%). In almost every country there has been noticed in the last decades a tendency toward greater mortality due to such cause, and Costa Rica is no exception to the rule. The quinquennial mortality rate from 1916 to 1940 has climbed from 84.7 per 100,000 inhabitants to 122.3. Already it has been said that in our country the affections of the circulatory system occupy the first place among the causes of death in the population, if those under 5 years are excluded.[23] Moreover, the effect of the tropical location of the country provides distinguishing features of cardiological practice in this country, as we have been able to ascertain after more than 10 years' experience.

The climate has a favorable influence upon the rarity of cardiac complications in goiter. Classical exophthalmic goiter prevails in regions that have a continental climate, but not in those of a maritime climate, such as exists in our country. On the other hand, the same as in the mountainous countries of Europe, endemic goiter is not at all rare, it being known that the inhabitants of the high valleys are predisposed to suffer from it.

It is also probable that climatic factors are related to the rarity of bacterial endocarditis, either by modifying the microörganism's virulence or enhancing the host's resistance. The local frequency of parasitism and the carelessness of the inhabitants open wide doors to infections such as pyodermatitis and oral sepsis. By such means perhaps the immunity to the microbes commonly causing the bacterial endocarditis is increased.

The climate, on the contrary, is unfavorable in its effect upon faulty nutrition, either through economic factors affecting the consumer or by directly modifying a subtle nutritional equilibrium in foods. The relative shortage or the high price of fats and its lesser consumption due to the warm climate probably is a factor in the rarity of myocardial infarction (in hospital patients), influencing in a favorable sense the evolution of coronary arteriosclerosis.

It is recognized that among the diverse causes of heart disease parasites hold a place. Precisely the tropical climate creates adequate conditions for the transmission of malaria, Chagas' disease, ankylostomiasis, to mention just a few tropical affections which might be accompanied by cardiac disturbances.

The following points deserve special comment: 1. Medical geography; 2. The frequent causes of heart disease; 3. The rarer causes of heart disease; 4. The heart in relation to some tropical diseases.

1. Medical Geography. The territory of Costa Rica is subject to 3 geographical factors—latitude, altitude and the two oceans—which affect its climatology materially.

This country is very near the equator; the capital, almost in the center of

the country, is situated approximately at 10° northern latitude. Therefore it must be classified as located in the inter-tropical zone. The low regions are formed by plains and virgin forest, but soon the mountainous spurs begin and reach above 12,000 feet at their highest altitude. Two parallel ranges divide the country into two watersheds which flow into the Caribbean Sea on the East and the Pacific Ocean on the West. The width of the country varies from 70 to some 170 miles. The mountains run from northwest to southeast. Two large rivers surround the central plateau that shelters the greatest part of the population, its climate being better fitted for the development of human activities. These data will help to explain the climate in relation to atmospheric temperature, barometric pressure, evaporation, sunshine, humidity, clouds, wind and rain.[35]

*1. Air Temperature.* Hot on the coasts as expected at this latitude, it is refreshed by sea breezes, not yet well studied. The temperature is highest in the low regions in which the sea influence is small, and starts to fall with altitude. The territorial block, for reasons stated, is not subject to the sudden variations of temperature of those regions more distant from the equator and properly continental.

*2. Barometric* Pressure. Pressure diminishes with elevation but it remains very stable because of the absence of the disturbances of the continental masses.

*3. Evaporation, sunshine, humidity.* These factors are greatly influenced by latitude. It has been rightly said that a tropical sun is always a tropical sun. The altitude is of little influence apparently, although we have no definite figures on this matter.

*4. Clouds.* Generally the sky is clear in the morning, but soon becomes cloudy with an excessive evaporation.

*5. Winds.* The changes of the air masses between the hot ground and the upper atmospheric layers and the influence of the slopes of the mountains foster winds on the plateau, not thoroughly known, which appear to be an important factor in the local variations of the climate. On the other hand, trade winds blow continually from the northeast, laden with the oceanic refreshing humidity. Winds from the south blow at different periods; their influence is not clear.

*6. Rain.* The direction of the mountain range, perpendicular to that of the northeastern winds, remarkably influences the quantity of water which is precipitated on the Caribbean watershed, where the rainy season is practically continuous. The precipitation on the rest of the country obeys a more obvious rhythm, the rainy months are from May to November and the dry season follows during the balance of the year. The type of rain is that brought by the northeastern winds: brief, abundant, stormy.

In short, we can say that although Costa Rica is placed among the regions of hot climate, it offers, depending on the watershed, either the type of equatorial climate without any true dry season, the biological characteristics of which include among others richness of vegetation and intense parasitism; or the type of tropical climate with a dry summer and a rainy season in the winter. Besides, the central plateau enjoys the characteristics of the mountain climate of the hot regions: little temperature variations (average 68° F.), absence of a stimulating rhythm with that sweetness of the perpetual Spring which conceals the somnolence of the mind and of the senses.

The altitude of the plateau varies between 3,000 and 8,000 feet. However, the view that this elevation above sea level may constitute an unfavorable factor for the circulatory system is not supported by clinical observation. Peo-

ple adapted to the plateau are seen to be clearly differentiated in their vascular reactions from subjects who have been suddenly transported to considerable heights or who are submitted to barometric variations in air chambers.

2. The Frequent Causes of Heart Disease. The fundamental causes of heart disease can be summarized into 4 etiological groups: sclerosis, rheumatism, syphilis and cardio-pulmonary. These comprise almost 90% of the types found post-mortem. In the sclerosis group we include calcific aortic stenosis, aortic atheroma, generalized arteriosclerosis, coronary arteriosclerosis, myocardial infarction and generally the so-called cardio-renal group. In the rheumatic group are included all valvular lesions except the syphilitic and calcific aortic stenosis. But due to etiologic doubts[19] concerning aortic stenosis with calcification of the valves, we have made a sub-group of these cases plus those properly rheumatic. In the syphilitic group are included syphilitic aortitis and aortic aneurysm. In the cardio-pulmonary group are classified heart failure secondary to a pulmonary disease, bronchiectasis in most of the cases.

In Table 1 we present data gathered in our study of 8000 necropsies.

We have been much impressed by the few cases that were found of myocardial infarction, only 23 (0.2%) of the total number of autopsies. Master[24] concludes that in the United States 114,000 persons die annually from coronary artery disease. Holoubek[16] in the South of the United States, in a comparable group of 8313 autopsies found 117 cases whose death was due to myocardial infarction and, or, coronary occlusion (an incidence of 1.4%).

We may safely conclude that coronary artery disease and acute coronary thrombosis do not have among hospital patients an importance comparable to that of northern countries. It is possible, of course, that the important factor to which this phenomenon might be due is a diet poor in fats, related to adverse economic factors affecting the population served by hospitals, and to the lessened caloric requirement in a mild climate.

Contrary to what has been declared by authors without tropical cardiological experience, rheumatic heart disease is fairly frequent. It seems to us unquestionable that bad hygienic living conditions of a great sector of the population determine its incidence. Holoubek's[16] figures are less than our own, 15.6%. The same is true of Scott and Garvin's[32] in Ohio. Clawson[5] in Minnesota, among 30,265 autopsies finds 18.6%. Additional studies on this subject have been published elsewhere.[9] We can conclude by saying that climate by itself does not possess preventive or curative virtues for rheumatic cardiopathies.

The frequency of syphilis might seem relatively high. However, it is less than that found in other countries of similar racial and social characteristics.[11] For instance in Puerto Rico, Koppisch[21] reviewed 1259 autopsies, finding an in-

TABLE 1.—FREQUENT CAUSES OF CARDIAC DEATHS IN COSTA RICA

| Etiology | % of all Autopsies | % of Cardiac Deaths | Females | Males |
|---|---|---|---|---|
| Sclerosis | 4.4 | 45.1 | 118 | 238 |
| Rheumatism | 1.7 | 18.6 | 53 | 86 |
| Rheumatism & Calcific Aortic Stenosis | 1.9 | 20.0 | 59 | 100 |
| Syphilis | 1.8 | 19.1 | 27 | 120 |
| Cardio-Pulmonary | 0.4 | 5.0 | 16 | 23 |
| | | | 273 | 567 |

cidence of 10% of all forms of heart disease, of which syphilis was the most important cause, being found in 30% of the cardiac cases. Among our people a high percentage of negro patients who died from this cause is observed. The incidence of negroes with syphilitic heart disease is 31.9%, much higher than in any other form, the percentage of negroes among the total cardiovascular mortality being only 17.5%. Excluding this race, the incidence of cardiovascular syphilis is reduced to 13%.

3. The Rarer Causes of Heart Disease. These less frequent causes of heart disease represent 11.4% of the total cardiovascular mortality reviewed. Excluding those affections rare by themselves and the uncertain cases due to lack of data in the autopsies and clinical study, 2 important sub-groups remain. The first is that of causes rarer in other countries, chiefly anemic and nutritional heart disease. The second is that of causes more frequent in other places, especially sub-acute bacterial endocarditis (See Table 2).

TABLE 2.—RARER CAUSES OF HEART DISEASE IN COSTA RICA

| Groups | Etiology | Cases |
|---|---|---|
| 1. Lack of Data | Unknown | 13 |
| 2. Rare Types | Myocardial Abscess | 1 |
| | Cysticercosis of the Myocardium | 1 |
| | Necrotic Post-partum Myocarditis[15] | 1 |
| | Pericarditis | 7 |
| | Rupture of the Aorta | 1 |
| | Tumor of the Heart | 2 |
| 3. Rare Types in Other Countries | Anemia | 18 |
| | Ankylostomiasis | 10 |
| | Ankylostomiasis & Nephrosis | 1 |
| | Malnutrition & Hepatic Cirrhosis | 5 |
| | Malnutrition & Tuberculosis | 4 |
| 4. Frequent Types in Other Countries | Congenital Heart Disease | 7 |
| | Fatty Infiltration of the Heart | 1 |
| | Bacterial Endocarditis | 21 |
| Total | | 93* |

* 6 cases duplicated in Table 1.

A review of recent studies made on myocardial syndromes of uncertain etiology reveals that authors do not agree on terminology or pathogenic implications.[14] One may conclude that the so-called isolated myocarditis (Fiedler's) is not the best inclusive term for such a heterogeneous group of diseases. A new approach toward the possibility of myocardial damage produced by allergic and metabolic disturbances, including malnutrition, is evident. The cases associated with hepatic cirrhosis seem to us[10] particularly revealing in view of the fact that cirrhosis has been mentioned as associated with beri-beri heart disease in alcoholics. Besides, there has been recently much insistence upon deficiency factors in the etiology of cirrhosis of the liver. Clinically these cases can be diagnosed as myocardial fibrosis, as the autopsy findings show zones of fibrosis in the myocardium and endocardium with parietal thrombus formation and frequently far reaching embolization.[6,33] Although our study has been made among subjects living in conditions of relative malnutrition it is surprising that the number of cases is not higher. It is possible that many such patients who die of intercurrent diseases are classified under tuberculosis, pneumonia, and so on.

More frequently we observe clini-

cally and in the necropsies anemic heart disease due to the high incidence of ankylostomiasis. We shall refer to this affection later.

It is known that bacterial endocarditis in its acute form is usually very rare. In our material we found only 2 such cases. As it may appear in the course of many infectious diseases and this particular group of cases was not surveyed, our statistics are incomplete, so we shall take under consideration only 19 cases of the subacute variety.

P. D. White[37] says that subacute bacterial endocarditis occurs in about 5% of cases of rheumatic heart disease and he supposes "that in communities where rheumatic heart disease is infrequent the predisposing factor of congenital defects is as important as is that of rheumatic valvular disease, and in such communities one would expect to find the total incidence of subacute bacterial endocarditis considerably reduced in comparison with that in rheumatic areas". Among our cases, on the contrary, there stands out only one case of endocarditis upon a congenital lesion opposing the total cases of rheumatic heart disease. Our incidence of subacute bacterial endocarditis is 2.7%. Holoubek[16] gives a figure of 4.7%. Kean,[20] analyzing 14,304 autopsies among workers in the Canal Zone, Panama, gives figures like ours: 2.8% (when Americans are included: 3.7%).

In Holoubek's[16] statistics approximately half were negroes; in Kean's[20] series 63.3% of the total were negroes. In ours there was only one doubtful case, so we minimize the racial factor.

We believe that, contrary to current medical thinking,[29] the presence and persistence of known focal infection in rheumatics in some way protects them from bacterial endocarditis. It is only among those rheumatics who take excessive care of themselves by eradicating all possible foci of infection, or who by chance come in contact with more virulent organisms, that a secondary bacterial endocarditis is likely to develop. It is a fact that the rheumatics we meet every day in hospital practice never bother about prophylaxis. And the same is probably true regarding the poor population of the Southern United States or the tropical workers in the Panama Canal Zone (See Table 3).

TABLE 3.—DEATHS FROM RHEUMATIC HEART DISEASE AND BACTERIAL ENDOCARDITIS IN NORTH AND CENTRAL AMERICA

| Authors | Cardiac Deaths | % Rheumatism | % Bacterial Endocarditis |
|---|---|---|---|
| Clawson, Minnesota | 4678 | 18.6 | 11.0 |
| García Carrillo, Costa Rica | 768 | 20.0 | 2.7 |
| Holoubek, Louisiana | 1045 | 15.6 | 4.7 |
| Kean, Canal Zone, Panamá | 2497 | — | 2.8 |
| Scott & Garvin, Ohio | 790 | 15.1 | 5.6 |

We recall that Libman and Friedberg[22] deal with the immunization problem as follows: "A trial of prophylactic immunization of patients with acquired valvular and congenital heart disease seems indicated since the usual causative organisms in the persons affected are known. The difficulty lies in the absence of immunologic tests to determine whether any immunity has been effected".

To close this section let us point out that significant fatty change of the myocardium is an exception, only 1 such case being found in our material.

4. The Heart In Relation To Some Tropical Diseases. We do not find in this series of autopsies any case of myocarditis due to Chagas' disease or to malaria. But as no special research was done in malaria it can not be ascertained what was the incidence of myo-

carditis or what may be its relation to anemic heart disease.

There is no evidence in favor of valvular lesions being produced by malaria, but in certain cases of the so-called pernicious attack, sudden death may occur. Generally it happens to be a paludic case with high fever, pallor or cyanosis, dyspnea, profuse sweating, delirium, precordial anguish or pain, rapid, irregular and small pulse, weak heart sounds, arterial hypotension. On necropsy the heart capillaries have been found full of malarial parasites.[18]

In advanced cases of malaria or ankylostomiasis heart failure can result, as has been observed by many authors with experience in severe anemias. In such cases the red blood cells amount only to 1 or 2 millions, sometimes around 500,000 per cu. mm. The hemoglobin is commonly only 30 or even 10% of the normal. The heart is enlarged and a gallop rhythm is present; apical systolic murmurs are frequent and even aortic diastolic murmurs can be heard.

The pathologic anatomy of the heart in fatal ankylostomiasis has been described by Calmette and Breton[2] as follows: "Within the pericardial cavity an abnormal quantity of fluid, sometimes slightly hemorrhagic, is found. The heart is flaccid, dilated, the walls of the ventricles are thin and show fatty degeneration. The right cavities as well as the left in certain cases, are full of fibrinous clots. Occasionally clots are also found in the cranial sinuses." We believe that the tendency towards phlebothrombosis that has been observed[31] among ankylostomiatics is due at least to a great extent to relative immobility. Sudden death due to massive pulmonary embolism, or to several small emboli followed by pleuropulmonary complications is not infrequent.[12] It seems quite possible that they impose a burden on a heart already strained by the anemia and nutritional deficiencies. The often fatal cardio-pulmonary syndrome of the ankylostomiatic can thus be integrated. Its prophylactic treatment, by correcting incipient heart failure and prescribing slight excercise, might decrease somewhat the high mortality due to hookworm infection in the tropics.

Chagas' disease[8] generally starts by the sting of an insect of the *Triatoma* species, especially in the face, or by contamination with its excreta which introduces the trypanosomes into the circulation. The initial sign is cutaneous, frequently a unilateral palpebral edema with dacryoadenitis and secondary adenopathy called the opthalmoganglional complex, which nevertheless is not pathognomonic. The cardiac evolution of the acute cases is manifested above all by a sinus tachycardia not related to the temperature, generally moderate and unstable, with a certain predilection for occasional premature contractions. In some cases the radiography reveals a slight or moderate increase of the cardiac silhouette. The electrocardiogram shows changes in the shape of the waves, especially the T wave and the ST segment. The anatomo-pathological study of the heart shows intense proliferation of histiocytes, infiltration of leukocytes and lesions of the muscular fibers, atrophy or fatty degeneration. The trypanosome, in the form of leishmania, can be seen in the myocardium. Lesions of the valvular endocardium are not known to exist.

This trypanosomiasis has been described in Costa Rica since 1941[36] and several cases have been well studied.[3] When the disease enters a chronic stage due to reinfection or to evolution of the organisms inside the body, a chronic cardiopathy can conceivably exist; but we have no experience on such cases. Usually it is the picture of myocardial fibrosis, the etiological diagnosis of which is based upon a specific

complement fixation reaction. Neither do we have experience with other diseases which may be seen in the tropics and be complicated by myocarditis, such as typhus fever, yellow fever, echinococcus disease, infestation with other parasites and so on.

To the observer in the tropics, the accidents produced by the bites of venomous snakes are impressive and well described in medical literature.[1,25,27] Well known are the weakness of the heart during the envenimation and the production of cardiac lesions.[26] As it seems that serial electrocardiography has not been carried out in the course of such poisoning, we shall now speak of our opportunity to study 11 subjects on whom 25 electrocardiograms were taken.

Our snakes belong to the *Bothrops* species, which predominate in Central and South America.[28] Statistics[4] show that some 23 snake bites per 100,000 inhabitants happen annually in Central America. In 8,000 autopsies which we surveyed only 10 cases were found of death due to snake bite, and the snakes involved were practically always *Bothrops atrox* or *Bothrops schlegelii*. The most important finding in these patients consists of multiple hemorrhages. In the cases reported by us[13] these occurred frequently in the gastrointestinal tract and in the brain as well as in the renal pelvis. In one patient, aged 67, a cardiac dilatation was noted, but the most common lesions in the heart were sub-endocardial and subepicardial petechial hemorrhages which were prominent in 3 cases. Pulmonary congestion and edema were mentioned in 5 autopsies.

Cardiac alterations would be due to the action of cytolysins,[27] but the heart is also affected by disturbance of its nervous equilibrium or of its internal medium (homeostasis), effects which are not infrequent in the complex action of venoms. Houssay and Mazzocco[17] showed that muscle treated by dilutions of snake poison has an abnormal permeability characterized by loss of certain elements such as phosphorus and, even more, potassium. This liberation of potassium recalls that of hemoglobin; that is, there is analogy between the action on the muscle and the hemolysis of red cells. This parallelism is interesting in considering the interpretation of the electrocardiogram, because today we know that this record in man can be modified in accord with the level of potassemia.

From the evidence gathered,[13] it can be concluded that in cases of snake bite associated with toxic phenomena the electrocardiographic pattern is the same in every case and consists of T waves of relative low amplitude and rounded apex, in one or more leads, and slight depression of the ST junction in precordial lead CR5 with prolonged QT. When the snake bite is not followed by toxic symptoms, these modifications are non-existent or very slight but of the same nature.

**Summary**. This article deals with a study of cardio-vascular disease made in the Republic of Costa Rica, based upon the analysis of 8,000 autopsies.

A mortality rate of 9.6% attributable to this cause was found. The sclerotic form of heart disease, including the so-called cardio-renals, amounted to 46.1% of the cardio-vascular deaths. Rheumatic heart disease contributed 20%, including aortic valve calcific disease. Syphilitic heart disease gave a rate of 19.1% when negroes are included, and only 13%, excluding this race. Cardiopulmonary heart disease amounted to 5.0%. In the group of rarer causes are mentioned affections due to malnutrition, ankylostomiasis and snake venoms.

We stress the rarity of myocardial infarct (0.2% of the total autopsies) and of sub-acute bacterial endocarditis. In explanation, factors of nutrition and

the mode of living of those people who attend hospitals are pointed out.

The climate of the tropics influences certain aspects of cardiological practice. To bring this out, reference is made to the climatology of Costa Rica and the relation of climate to parasitic diseases affecting the heart, in particular malaria, ankylostomiasis and Chagas' disease. In regard to ankylostomiasis we define the cardio-pulmonary syndrome which marks in some cases the end of this helminthiasis.

The effect of poisonous snake bite on serial electrocardiograms was studied. In the most serious cases a pattern which consists of T waves of relative low amplitude and rounded apex in one or more leads with a slight depression of the ST junction in precordial Lead CR5 and prolonged QT interval was discovered. It is suggested that these anomalies might be due to hypopotassemia.

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# THIOUREA COMPARED WITH PROPYLTHIOURACIL IN THE TREATMENT OF THYROTOXICOSIS

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Although thiourea was one of the first anti-thyroid drugs employed clinically, it was soon superseded by other compounds. Its early decline in popularity may be attributed both to its supposed low potency as indicated by animal assay, along with a high incidence of side reactions in the dosage originally employed (1 to 2 gm. daily). The data, herein presented, were accumulated in order to compare the clinical usefulness of thiourea in small doses with that of propylthiouracil.

Patients consisted both of staff cases and private patients followed by members of the staff. In keeping with the practice of Danowski, iodine was given along with the thiourea in almost all instances (15 min. Lugol's sol. daily). A minority of patients on propylthiouracil received iodine. It is the contention of Danowski's group that iodine enhances the therapeutic response of the drug. Others believe that there is a slight impairment in rate of improvement,[7] or no significant difference.[8] The present study does not provide evi-

TABLE 1.—THERAPEUTIC RESULTS

| | Average daily dose (grams) | Average time for complete control (weeks)* | Patients requiring greater dose for control† | Number showing overdosage effects | Number of cases receiving this dose anytime |
|---|---|---|---|---|---|
| Propylthiouracil | 0.1 | 5.0 (7) | 19% (7) | 0 | 19 |
| (38 cases) | 0.2 | 3.7 (14) | 8% (3) | 0 | 22 |
| | 0.3 | 4.0 (2) | 3% (1) | 0 | 4 |
| Thiourea | 0.1 | 10.0 (1) | 12% (5) | 2 | 10 |
| (41 cases) | 0.2 | 4.7 (8) | 5% (2) | 2 | 20 |
| | 0.3 | 5.5 (24) | 0 (0) | 1 | 27 |

* This average was obtained only from those patients who *responded* to an *initial* dose of the stated magnitude. The number of cases is in parenthesis.

† Percentages are in terms of total series. These patients were evaluated 3 to 8 months after initiation of the stated dose. Also are included those who relapsed when previous higher doses were reduced to this level. In parenthesis are number of cases not controlled at this dose.

Danowski and co-workers, however, have found the compound to be a very effective and non-toxic drug when given in doses of 0.025 to 0.3 gm. daily.[4,5,16] Moreover, Astwood has recently shown that in the human subject thiourea is actually somewhat more potent than propylthiouracil in its capacity to inhibit the synthesis of thyroid hormone.[13]

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dence on this point, except that iodine most certainly did not prevent a positive response to either drug.

**Efficacy of the Drugs.** Table 1 summarizes the therapeutic results. No patients were included in this tabulation who did not have perfectly typical hyperthyroidism, or who were not followed carefully enough to assess therapy. Complete control is defined as restitution of metabolic rate and pulse to normal, along with distinct weight gain and subsidence of subjective symptoms.

The data suggest that a dose of 0.2 or 0.3 gm. daily of either drug results in more rapid improvement than 0.1 gm. There is no doubt, however, that thiourea is effective in doses as low as 0.1 gm. daily. This dose in some instances is actually too high for continual maintenance. The figures on overdosage are not susceptible to statistical comparison because one always attempts to forestall overdosage by reduction of intake to the minimum which is required. One patient was not completely controlled on 0.3 gm. propylthiouracil and, in general, the dose required for complete control averaged somewhat higher than with thiourea. It will not be justified, with the data at hand, to attempt any precise comparison of potencies of the 2 drugs; however, it is fair to conclude that their clinical efficacy is of similar magnitude.

In 4 cases receiving 0.1 gm. to 0.2 gm. propylthiouracil and 2 cases receiving 0.2 to 0.3 gm. thiourea plus Lugol's solution, the gland became slightly but measurably smaller, but one patient getting 0.2 gm. propylthiouracil and one on 0.3 gm. thiourea plus Lugol's showed a distinct increase in the size of the thyroid, and the gland also became softer in consistency. In the latter instance, the enlargement was 2 or 3 fold and a bruit appeared. Regression followed cessation of treatment. The remaining patients of the combined series showed no apparent changes in the gross size of the thyroid.

Exophthalmos, if present, was measured in most instances and was not consistently altered to any great extent in either direction by treatment.

**Toxicity.** In Table 2 "proved reaction" denotes that reduplication of the effect was readily obtained by readministration of the drug. A "possible reaction" is one which occurred during treatment and promptly disappeared upon withdrawal of the drug, but following which no subsequent test dose was given. Neither drug produced agranulocytosis or any other dangerous complication. Side effects, such as fever, rash, and nausea were considerably more common with thiourea. Three instances of proved fever due to the latter drug (0.3 gm. daily) occurred after 10, 14, and 14 days respectively. The case of fever classed as "possible" was encountered after 9 days on this same dose and the "possible" rash occurred after a similar interval on 0.2 gm. daily. Nausea, which was seen mainly with thiourea (0.2 to 0.3 gm.) appeared immediately after treatment was started and necessitated discontinuance of the drug.

It should be mentioned that 2 of the

TABLE 2.–NUMBER OF CASES SHOWING TOXIC REACTIONS

| | | Nausea | Fever | Rash | Leukopenia | Agranulocytosis | Total Cases |
|---|---|---|---|---|---|---|---|
| Propylthiouracil | Proved | 0 | 1 | 0 | 0 | 0 | 1 |
| (51 cases) | Possible | 1 | 0 | 0 | 1 | 0 | 2 |
| Thiourea | Proved | 1 | 3* | 1* | 0 | 0 | 4 |
| (49 cases) | Possible | 2 | 1 | 1 | 0 | 0 | 4 |

* One case had both fever and rash.

patients who had received thiourea (0.2 gm.) and iodine for several months developed unexplained fever, swollen, painful joints, and myalgia which persisted for 14 to 21 days after the drug was stopped, but no fever could be induced later by test doses of either the drug or iodine. Another patient showed non-thrombocytopenic purpura, which was not affected by discontinuance or resumption of 0.2 gm. daily at intervals of several weeks. The drug was then discontinued, however, and eventually the purpura cleared with no recurrence after more than a year. It is impossible to say whether these 3 cases represent unusual toxic reactions.

The single febrile episode due to propylthiouracil appeared after 9 months of medication (0.1 gm. daily). Fever was reproduced on 4 subsequent occasions by 50 mg. of the drug. The case of leukopenia is classed as a possible reaction because of a white count of 3600, polymorphonuclear leukocytes 33%, anorexia, dizziness, and headache 15 days after 100 mg. daily was started. All findings were normal 2 days after stopping the drug. The instance of nausea with propylthiouracil occurred immediately after starting 0.2 daily on two occasions. One tenth gram daily was tolerated with very little nausea.

**Relapse After Discontinuance of Drug.** Of 27 cases controlled by drug for 3 months to 2 years and later withheld from treatment, 21 relapsed, a rate of 77%. The 6 cases which did not relapse have been followed from 6 months to over 3 years. One does not find in the present data any correlation of relapse rate with age, size of gland, duration of treatment, severity of disease, or the type of gland (Table 3). The suggestion of less frequent relapse in cases of short duration is not statistically significant. In addition to a comparison of averages as recorded other statistical evaluation likewise showed no positive relationships. When relapse occurred it was clearly evident within an interval of 2 to 8 weeks.

**Preparation for Surgery.** Twenty-three patients were operated on after being treated with drug. Fifteen were judged to be completely controlled preoperatively, and this group had a postoperative course which was considered very smooth in every case. The remaining 8 patients were not brought under complete control before operation. Four experienced a rise in temperature and pulse judged to be excessive. Two of these were treated as mild storm and recovered. A third did not have a thyroidectomy, but died in typical storm after hysterectomy. She is included to illustrate the hazard of storm after the stress of surgery in incompletely controlled patients. It is clear from these experiences that there is no magic in preoperative preparation with anti-thyroid drugs unless adequate doses are

TABLE 3.—ANALYSIS OF REMISSION AND RELAPSE

| | | AVERAGES | |
|---|---|---|---|
| | | Pts. relapsing | Pts. not relapsing |
| Age | | 49 | 42 |
| Size of Gland | | "1.8 plus" | "1.6 plus" |
| Duration Disease | | 9 mo. ± 1.2* | 6 mo. ± 1.3* |
| Duration Treatment | | 8 mo. | 9 mo. |
| Percent of group with nodular gland | | 35% | 33% |
| Percentage distribution | Mild | 20% | 17% |
| according to severity | Moderate | 40% | 33% |
| of disease | Fairly Severe | 25% | 33% |
| | Severe | 15% | 17% |

* St.E.—Standard Error

given for sufficient time to insure complete remission.

Table 4 summarizes difficulties encountered with excessive bleeding and friability at operation, along with an appraisal of the histological state as judged by the pathologist. As would be expected, iodine given with or after the drug reduced the incidence of excessive hyperplasia, although involution has frequently been incomplete. It may be noted that in 10 cases receiving iodine alone, which are included for comparison, involution, even here was by no means complete. In general, the histological state of the gland after iodine plus drug was not materially different from that after iodine alone.

**Comments.** The above observations confirm the effectiveness of thiourea in low dosage. The incidence of side reactions was, however, higher than reported by the New Haven group who encountered only 2 cases of fever in 120 treated cases.[5] The low toxicity of propylthiouracil is in agreement with the experience of others.[1,3,6-11,14] The present series, combined with cases obtained from the literature, gives an over-all incidence of proved or suspected side reactions of 270 in 960 cases, and only one case of agranulocytosis was seen in the combined series. It may be concluded that thiourea is inferior to propylthiouracil in its higher incidence of side reactions, although major complications, such as agranulocytosis, have not as yet been met with during use of thiourea.

The reported frequency of relapse after termination of drug therapy varies from 33 to 62%.[2,6,8,15] The over-all average in 225 reported cases, including the present series, is 55%. The present data do not bear out the impressions of others that relapse is less frequent in the presence of a small gland or in mild cases of the disease.[2,12,15]

**Summary.** 1. Most patients given thiourea were controlled by doses of 0.1 to 0.3 daily. Side reactions, chiefly fever, occurred in 16% of cases; no dangerous toxicity was encountered.

2. In 51 cases treated with propylthiouracil there was 1 instance of fever, 1 of mild leukopenia, and 1 of nausea. Complete control of thyrotoxicosis occasionally required doses in excess of 0.3 gm. daily.

3. Iodine given with an antithyroid drug did not interfere with its efficacy and produced an involution of the gland similar to that seen after iodine alone.

4. Relapse rate in 27 cases after withdrawal of drug was 77%. No factors were discovered which allowed prediction of a sustained remission in a given patient.

TABLE 4.—ANATOMICAL CONDITION OF THYROID GLAND

| | NUMBER OF CASES | | | | |
|---|---|---|---|---|---|
| | Total | Technical operative difficulty | Gland predominantly hyperplastic | Evenly mixed hyperplasia & involution | Predominantly involution |
| Drug alone | 7 | 4 | 4 | 1 | 2 |
| Drug plus iodine or followed by iodine | 15 | 1 | 4 | 5 | 6 |
| Iodine alone | 10 | 1 | 3 | 3 | 4 |

We are grateful to those members of the staff who have furnished data on private patients for inclusion in this study. We are also indebted to Dr. Stanton M. Hardy of Lederle Laboratories and Dr. L. E. Josselyn of Abbott Research Laboratories for supplying the propylthiouracil which was used during the early part of the study.

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# CONCENTRATED ROENTGEN THERAPY OF CERVICAL TUBERCULOUS LYMPHADENITIS

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The roentgen therapy of tuberculous adenopathy, especially the cervical form, is a well established procedure within radiology, although it is somewhat less known as an efficacious treatment in the various branches of the medical profession which are the source of the radiologist's patients. Although reports on the excellent results secured by this form of therapy have appeared periodically in the radiological and other medical literature, the present time seems appropriate to reaffirm several points in connection with the treatment of this disease as well as to present the advantages and results of a concentrated technique of irradiation. The introduction of streptomycin as treatment for tuberculous involvement in various parts of the body raises the question as to the present status of roentgen treatment of tuberculous adenopathy. The purposes of this report are: (1) to re-emphasize the high quality of results secured by roentgen therapy, (2) to point out the advantages in time and convenience of our particular plan of treatment, and (3) to contrast the results of roentgen therapy with streptomycin in the treatment of the tuberculous adenopathy.

Study has been limited to cases of cervical tuberculous lymphadenitis, since this group is numerically large enough to furnish a satisfactory basis for analysis, although tuberculous adenitis in other parts of the body, notably the inguinal and axillary areas, is treated by us and known to respond to irradiation. During the period 1939-1947, 42 cases of cervical tuberculous lymphadenitis were accepted for treatment in the Therapy Division of the Department of Roentgenology, University of Michigan Hospital. Of these 42 cases, treatment was completed and follow-up was considered adequate in 37 cases and these form the basis of our study.

Diagnosis was confirmed by pathological or bacteriological material in 30 cases (80% of the series). The remaining 7 cases presented clinically characteristic features of tuberculous adenopathy, 3 having radiographic evidence of active or quiescent pulmonary tuberculosis and 1 having calcium in cervical nodes. Another patient had a life-long history of repeated suppuration and breakdown of cervical lymph nodes and in infancy and childhood drank milk from cows which were later ordered slaughtered because of tuberculous infection. In 2 cases such corroboratory evidence was lacking but the clinical course and response in every way justified the clinical impression. It must be emphasized that bacteriological or pathological proof of the clinical diagnosis should be diligently sought after in every case since confusion with non-specific cervical lymph-

adenitis, various other infections of the cervical nodes, thyroglossal or branchial cleft cysts, lymphoblastoma, or metastatic carcinoma can otherwise easily result.

*Roentgen therapy used.* The technique of treatment in these cases consists in using radiation generated at 200 kilovolts, filtered with 0.5 mm. copper and 1.0 mm. aluminum (half-value layer 0.9 mm. copper) at a target-skin distance of 50 cm. and at a rate of about 50 r per minute. Fields are large enough to include the obviously diseased nodes as well as the regional group and have varied from 8 x 10 cm. up to 15 x 15 cm. Treatment is given daily, 200 r (measured in air) to one field, for 4 or 5 days. In the case of children or debilitated adults 100 to 150 r to one field is given. Usually total dosage is 800 to 1000 r per field and at completion the patient is asked to return in 2 to 3 months. An occasional patient is given a second course at that time. If good regression does not follow the second course, the response is considered unsatisfactory and further irradiation is not given.

The reactions ensuing from this method of irradiation are insignificant. Slight soreness in the throat may appear but is transient. The acute reaction in the skin is essentially negligible. No late cutaneous damage has been seen even when 2 courses were given. Even radiation pigmentation is minimal or, more often, absent.

The experiment of employing a radiation technique concentrated in respect to time as opposed to the traditional protracted method was motivated by the practical inconvenience of the latter and an undesirable incidence of definite (sometimes severe) radiation damage of the skin. Multiple intermittent irradiations over a protracted period may produce significant to severe radiation changes while larger doses (within certain limits) given in a short time and never repeated will result in lesser degrees of permanent tissue change. It is of interest that in the cases reported here there is only one in which evidence exists to suggest suppuration induced by irradiation. In this patient with a small solitary lymph node of 1 to 2 weeks duration, it was reported to us that the node became fluctuant 1 month after treatment and that aspiration was performed with subsequent regression of the adenopathy. It is an open question whether the suppuration in this case was the result of irradiation or spontaneous. Suppuration did not follow treatment in any of the other patients, many of whom had bulky masses of involved nodes.

Results were classified as satisfactory or unsatisfactory. Intermediate grades of improvement less than complete regression have all been grouped together as unsatisfactory since it was felt that anything less than complete regression is unsatisfactory when dealing with a chronic disease which is subject to regression over a long period of time even when untreated. On this basis of evaluation we have had complete regression in 31 cases (84% of the patients studied). Six patients (16%) were thought to show unsatisfactory response although there was some improvement in several after either one or two courses of treatment. Of the 31 patients showing complete regression, 23 had draining sinuses present at the inception of therapy, some of these sinuses having developed following biopsy or drainage of fluctuant masses. In the 6 cases where response was unsatisfactory, there were 4 with draining sinuses. From this it appears that the presence of draining sinuses has no particularly adverse effect on the results of radiation therapy. Conservative surgical procedures are advantageously combined with irradiation. Fluctuant masses on the verge of breakdown may be aspirated, if possible, or incised for diagnostic or therapeutic reasons. Radical neck gland dissections should play no part in the modern management of tuberculous adenopathy and can usually be avoided.[3]

Examination of our data shows that

there was a wide range of duration of the nodes prior to roentgen therapy, from several weeks to many years. In the 31 cases with satisfactory results, in about 26% the adenopathy had been present for 6 weeks or less, compared to approximately 40% in the small group of 6 cases with poor response to treatment. For the first group, 52% had nodes for 6 months or less, and 71% for 1 year or less; the respective figures for the second group are 60% and 66%. The differences of duration prior to treatment, in those cases responding well to irradiation and those that did not, cannot be deemed significant.

It is difficult to estimate the time in which regression of the diseased lymph nodes takes place. Because they have no further trouble, many patients do not return at the requested interval of 2 months. Some are seen only at later dates because other clinics in the hospital to which the patient applies for treatment of unrelated conditions months or years later refer them to us. Often a statement in the patient's record to the effect that no evidence of cervical adenopathy is found at the present date must be interpreted as complete regression but gives no indication of the time of clearing in relation to the treatment. Conversely, the patients with incomplete regression are those who are likely to return at the specified intervals for check-up. One can therefore only form an impression as to the time in which regression can be expected to take place; our impression is that when response is satisfactory, it is also early. In such cases, it is noted that regression begins in 2 to 4 weeks after completion of treatment. A minority of cases will diminish perceptibly but incompletely and continue their regression slowly after the second course.

In 1 patient in whom the follow-up course now extends over 5 years, complete regression ensued shortly after a course of irradiation. Three years later the appearance of enlarging nodes with abscess formation in the treated area brought the patient to another radiologist who was able to produce a prompt regression again. Two years following the second course the patient remains asymptomatic. This patient is an exceptional case and far from typical. Even though our follow-up in many cases extends over a 4 or 5 year period we have found that when exacerbation occurs it usually takes place early. Late exacerbation is so unusual that it raises the question as to whether it really is exacerbation or involvement of adjacent untreated areas. The latter situation can be expected to occur in a few cases where the extent of the disease is not apparent or misjudged at the time of treatment. This source of error will be minimized if careful examination is carried out in order to locate the fields of treatment correctly.

A review of the recent literature reveals a favorable comparison of the results secured by our plan of treatment with the best results secured elsewhere. Generally, plans of treatment elsewhere are extended over a period of a month to a year with total dosage per field as low as 450 r and as high as 1500 r per field, individual treatments of the series being given at intervals of a week to a month. The reason usually stated for such protraction of the treatment is that the chronicity of the disease and the experience of other observers requires such an approach as the best and safest treatment. For example, Hauser[2] secured satisfactory (50 to 100% regression during treatment or within a few months following) results in 88% of his series of cases with tuberculous cervical adenitis by treating at intervals of 10 days for a period of 100 days. These results are among the best reported and agree closely with our own. However, we accomplish this result by treatment on 4

or 5 successive days, in exceptional cases giving a second course 2 months later. This represents an important advantage to the patient in time and convenience and he is more likely to complete the course of treatment than if it is extended over months. Treatment may be given on an out-patient basis, in which case time lost from work or studies is at a minimum. In our series, only 7 of the 31 cases (22%) classified as showing complete regression required a second course of treatment over a specified area. By definition, the patients with incomplete regression or unsatisfactory response have all had more than one course of roentgen therapy.

The availability of streptomycin has led to its increasing use in treatment of various forms of tuberculous involvement, including tuberculous adenopathy. Our experience with streptomycin-treated tuberculous adenitis is limited, as in this institution nearly all such cases are treated by irradiation. To meet the third purpose of this study, therefore, we have relied chiefly on the recent reports[1,4] of the Council on Pharmacy and Chemistry of the American Medical Association. The Sub-Committee on Streptomycin assembled the observations on the use of this drug from widely scattered medical centers and their conclusions probably reflect the most authoritative and recent thinking on the use of specific therapy in tuberculosis and its complications. They found that the effects of streptomycin therapy on tuberculous sinuses have been sufficiently uniform to establish its usefulness. The underlying lesions in these cases were in bone, cartilage or lymph nodes. "A number of these patients have also had one or more groups of firm, non-caseating lymph nodes. The effect of streptomycin on these nodes has been variable. In some instances a definite and prompt reduction in size occurred, while in others there has been little or no change. There is no obvious reason for the disparity in these results."

In view of the toxicity of streptomycin, careful laboratory supervision and hospitalization are recommended during the course of treatment, which extends from 90 to 120 days. Anything less than a complete course is unjustified. The advantage of radiation therapy is obvious even if from this point of view alone. Results of treatment with radiation lend additional support to our belief that streptomycin therapy might best be reserved for the 15 to 20% of cases which are resistant to adequate treatment by roentgen therapy.

The indiscriminate use of streptomycin introduces the real danger of creating streptomycin-resistant tubercle bacilli. Such a risk is, of course, to be accepted in those forms of tuberculosis which carry a serious prognosis and for which no other adequate means of therapy exist. In cases of tuberculous adenopathy, where so often the disease is of limited extent and the results of irradiation may be so good, the possibility of producing streptomycin-resistant organisms should be avoided.

The report of the Sub-Committee on Streptomycin contains this carefully worded statement which is made without reference to radiation therapy but which must be interpreted as being especially significant in view of the excellent results secured by the radiologist in the treatment of cervical tuberculous lymphadenitis. "For the present, streptomycin should not be used in the treatment of minimal pulmonary tuberculosis or *other lesions that may be expected to clear on older and accepted forms of therapy.*"

**Summary.** Thirty-seven cases of cervical tuberculous adenitis treated by roentgen therapy and conservative surgical procedures and having adequate treatment and follow-up have been reviewed.

Complete regression of the diseased nodes and healing of sinuses occurred in 84% of the cases; in about 20% of these, a second course of irradiation was necessary to achieve this result. If the patient did not respond properly to the second course of roentgen therapy, no more irradiation was given. This latter group of cases, showing incomplete regression or an unsatisfactory result, comprises 16% of our series.

These results were secured by a plan of treatment extending over a period of 4 to 5 days in contrast with plans of treatment used in other clinics which call for protraction over a period of several weeks, months, or even a year. The advantages in time and convenience of our plan of treatment are obvious and results are comparable to the best reported in the literature.

For the present, at least, radiation therapy must be regarded as superior to streptomycin in the management of cervical tuberculous adenopathy. Streptomycin might best be reserved for use in the 15 to 20% of all cases where irradiation does not cause complete regression.

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# THE TRANSFUSION OF ARTERIAL HYPERTENSIVE AND NORMOTENSIVE BLOOD INTO HYPERTENSIVE SUBJECTS

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Many attempts have been made in the past to demonstrate the presence of circulating vasoconstrictor or pressor substances in the blood of hypertensive individuals. As early as 1911 Bröking and Trendelenburg[1], using frogs, found no greater vasoconstrictor activity in blood from hypertensive patients than in that from normal subjects. Likewise in that year, Stewart[12] did not find pressor effects in dogs injected with small amounts of serum from hypertensive patients. More recent investigations, consisting of direct transfusions of hypertensive blood from man to man by Höst,[6] failed to show pressor activity. Pickering[7] and Prinzmetal, Friedman, and Rosenthal[8] did not find any elevation in blood pressure when they transfused blood from patients with malignant hypertension into patients with a normal circulatory system, even when as much as 2000 cc. of blood was given.

The progressive changes in renal function and renal hemodynamics, associated with hypertensive disease in man are heralded in early stages by a reduction in effective renal blood flow. The rate of glomerular filtration, however, is usually within the normal range in this state. The ratio between glomerular filtration and the total renal blood flow is increased. In most cases of well established hypertension, there is present a diminution in the renal blood plasma flow and an increase in the filtration fraction. Other changes occur; the maximal tubular excretory capacity and the maximal tubular reabsorption may be reduced. Again, usually in the later stages of the disease, the glomerular filtration rate is reduced.[5]

The experiments here reported were made in an effort to demonstrate pressor or vasoconstrictor substances in the blood of patients with hypertension by using the kidneys of hypertensive individuals as test objects. It was thought that transfusion of blood containing pressor substances by bringing about efferent arteriolar constriction might produce in such individuals a transitory fall in renal blood flow and elevation of the filtration fraction over the pretransfusion values, whereas such changes might not occur following transfusion of normotensive blood.

Arterial rather than venous blood

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was used because of the possibility that destruction or inactivation of vasoconstrictor or pressor substances might occur during their passage through various arteriolar beds. In some experiments recipients with markedly impaired renal function were studied because of the possibility that the tissues of such patients might inactivate pressor substances more slowly than those of normal subjects.

**Methods.** Six hypertensive patients were each made the recipients of a transfusion of arterial blood from a normotensive donor and from a donor with hypertension. In 1 patient, H. C., normotensive venous blood was also transfused. Of the 6 hypertensive recipients the renal status of 1 was excellent, that of 1 was good, while those of 4 were poor, as evidenced by the clearance of mannitol and para-amino hippurate as well as other renal function studies. In the latter 4 cases there was nitrogen retention.

Suitable donors were typed, their Rh status determined, and their blood cross-matched with that of the recipient within 24 hours preceding the transfusion. Recipients and donors were in the fasting state at the time of the procedure. The glomerular filtration rate and the renal plasma flow were determined by measuring the plasma mannitol and para-amino hippurate (PAH) clearances, respectively. The clearance periods were usually of 20 minutes duration, but were sometimes longer during those periods when blood was being transfused.

In the first experiment, 75 cc. of 2% citrate solution was added to the infusion solution during the 2 pre-transfusion periods as a control; this practice was abandoned in later experiments. Toward the end of the second clearance period, arterial blood was collected from the brachial artery of the donor over the course of 15 to 30 minutes into a flask containing 75 cc. of citrate solution to prevent clotting. This arterial blood was substituted for a very slow intravenous infusion of 0.9 gm. % NaCl which was introduced during the first 2 periods. The other intravenous infusion, containing mannitol and sodium para-amino hippurate in approximately 0.7% solution of NaCl, was maintained at the same rate (4 cc. per minute) as in the preceding periods. Clearance measurements were then continued during 2 periods while the blood was transfused. Two hundred to 450 cc. of blood was introduced in 30 to 60 minutes. Subsequently, observations were made during 2 additional periods (Numbers 5 and 6). In some experiments the blood was replaced by 0.9% NaCl during periods of 5 and 6, the rate of flow being 4 cc. per minute; in other experiments this infusion was discontinued after period 4. An indwelling urethral catheter was used to facilitate collection of urine. Twenty cc. of distilled water and 20 to 50 cc. of air were introduced to insure complete evacuation of the bladder. Blood pressure readings were taken throughout the procedure by the auscultatory method except during one experiment when no observations were made. One group of experiments was done to follow specifically the effect upon blood pressure when blood was transfused into a hypertensive individual with renal insufficiency. Measurements of renal clearance were omitted in this experiment. No elevation in temperature occurred after any transfusion, nor were there other signs of unfavorable reactions.

The experiments were carried out under as similar conditions as possible in order to minimize physical or psychological influences. The same environment was used for all patients. The procedure was explained to the patient as an evaluation of the function of his kidneys. In a given recipient, exactly the same details of experimental procedures were followed using blood from a hypertensive donor as when using the control blood. The measurement of para-amino hippurate in blood and urine was conducted by the method of H. W. Smith and his associates.[10] The measurement of the mannitol was carried out by the method of W. W. Smith *et. al.*,[11] as modified by Goldring and Chasis.[5] The determined values of the clearances were corrected to the standard surface area of 1.73 sq. meters, on the basis of height and weight.[2] Techniques employed for calculating the "mannitol blank" varied during the course of this investigation.[4]

**Results.** There was a definite although slight trend upward in the diastolic pressure of all 5 patients after transfusions of hypertensive as compared to normotensive blood (Table 1). There was no consistency, however, in the changes in the clearances of mannitol or para-amino hippurate, or in the filtration fraction when arterial hypertensive or normotensive blood was transfused into 5 hypertensive patients. In some cases alterations in renal hemodynamics which were not duplicated after the transfusion of nor-

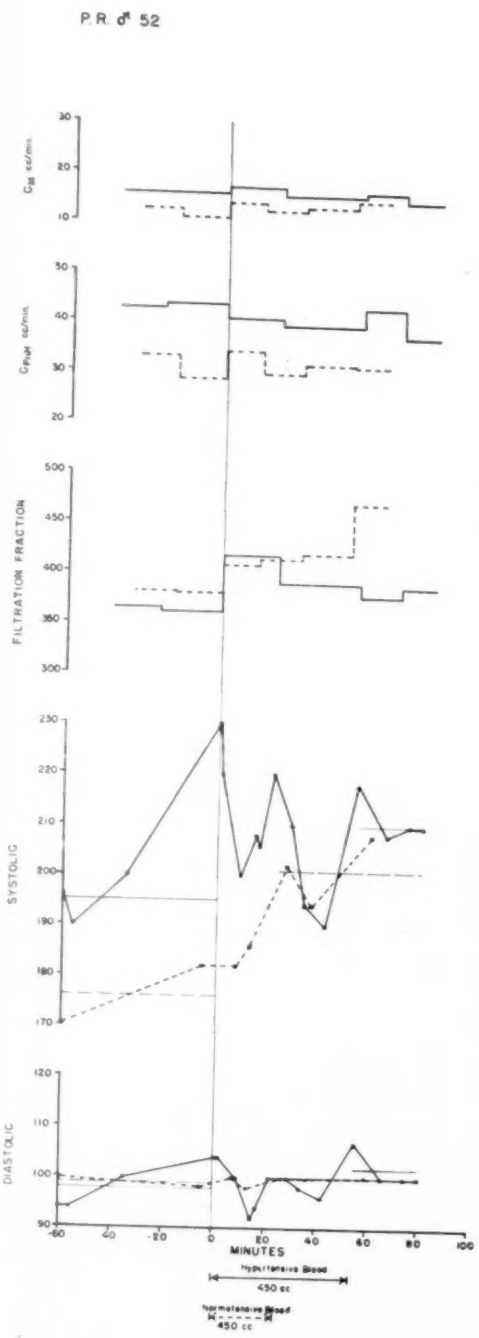


Fig. 1

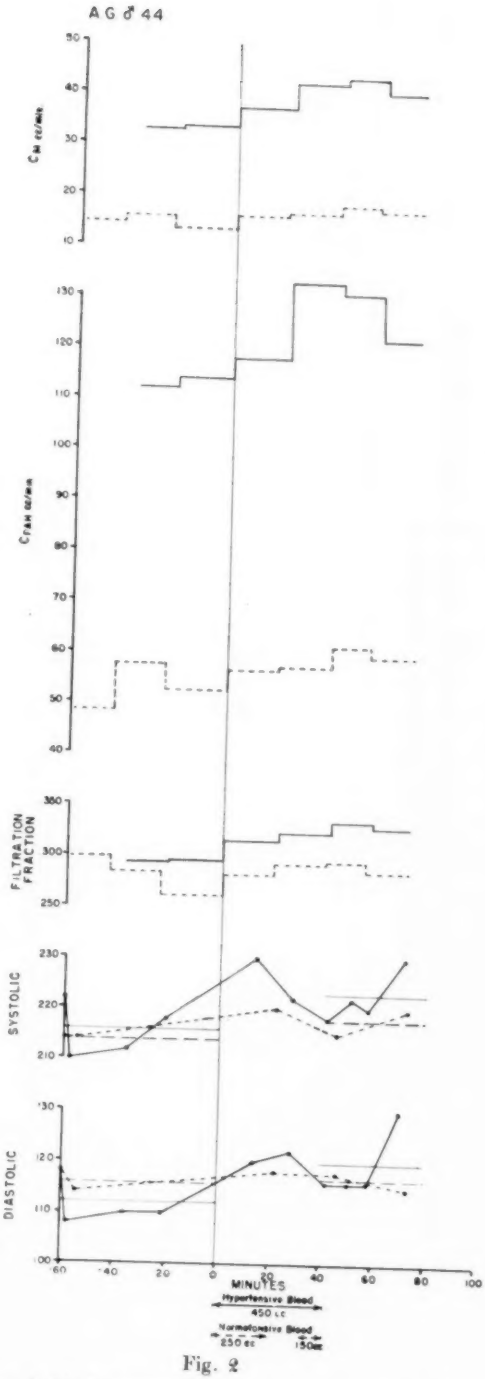


Fig. 2

FIG. 1.—Subject P. R. A comparison between changes in blood pressure, plasma clearance of mannitol, para-amino hippurate, and the filtration fraction after the transfusion of hypertensive and normotensive blood in patients with chronic glomerulonephritis in the uremic stage.

The vertical line at 0 minutes represents the beginning of the transfusions and the horizontal arrows represent their durations. $C_M$ and $C_{PAH}$ are the clearances of mannitol and para-amino hippurate respectively. Systolic and diastolic show blood pressure in mm. Hg. The horizontal lines represent averages for the periods indicated. In all figures the solid lines represent values obtained when hypertensive blood was used and the broken lines when normotensive was used.

FIG. 2.—Subject A. G.

## TABLE I.

## TRANSFUSION OF ARTERIAL HYPERTENSIVE AND NORMOTENSIVE BLOOD INTO HYPERTENSIVE SUBJECTS

| Recipient | | | | | | | Donor | | | | | | | Date of Experiment | Am't. Blood Transfused | Average Blood Pressure | | | Max. Change in Bl. Pr. | Max. Change in Plasma Clearance Per Cent of Control Value† | | | | Difference (Hypertensive minus Normotensive) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Initials | Age | Sex | Blood Group | Rh. | Diagnosis | Renal Function | Initials | Age | Sex | Blood Group | Rh. | Diagnosis | Bl. Pr. | | | Before | After | Change | | Period | Mannitol | PAH | Filtration Fraction | Diastolic Bl. Pr. | Mannitol % | PAH % | Filt. Frac. % |
| | | | | | | | | | | | | | *mm. Hg.* | | *ml.* | *mm. Hg.* | *mm. Hg.* | *mm. Hg.* | *mm. Hg.* | | | | | | | | |
| P.R. | 52 | M | A | Pos. | Chronic Glomerlo-nephritis | Poor | A.K. | 43 | M | A | Neg. | Hypertension | 230/120 | 4/21/47 | 450 | 195/ 98 | 201/102 | +15/+ 4 | +23/+10 | 6 | − 8 | −13 | + 8 | + 9 | −35 | −15 | −15 |
| | | | | | | | L.F. | 41 | F | A | Pos. | Normal | 130/80 | 5/19/47 | 450 | 176/ 99 | 201/100 | +25/+ 1 | +32/+ 1 | 6 | +27 | + 2 | +23 | | | | |
| A.G. | 44 | M | O | Pos. | Chronic Pyelo-nephritis | Poor | L.M. | 38 | M | O | Pos. | Hypertension | 200/135 | 6/13/47 | 450 | 211/112 | 223/120 | +12/+ 8 | +19/+18 | 4 | +30 | +18 | +10 | +16 | +15 | + 9 | + 5 |
| | | | | | | | N.P. | 36 | M | O | Pos. | Normal | 118/80 | 6/27/47 | 250 | 214/116 | 218/117 | + 4/+ 1 | + 6/+ 2 | 4 | +15 | + 9 | + 5 | | | | |
| B.B. | 23 | M | O | Neg. | Chronic Glomerulo-nephritis | Poor | L.S. | 42 | F | O | Neg. | Hypertension | 220/98†† | 4/ 5/48 | 350 | 177/111 | 197/129 | +20/+18 | +27/+25 | 4 | +18 | +16 | + 2 | +13 | + 9 | + 8 | + 1 |
| | | | | | | | H.L. | 24 | M | O | Neg. | Normal | 110/70 | 4/12/48 | 350 | 178/112 | 184/119 | + 6/+ 7 | +12/+12 | 4 | + 9 | + 8 | + 1 | | | | |
| H.C. | 40 | M | A | Pos. | Chronic Glomerulo-nephritis | Poor | L.M. | 39 | F | A | Pos. | Hypertension** | 212/118 | 10/14/47 | 350 | 210/117 | 206/119 | − 4/+ 2 | + 2/+ 3 | .. | .. | .. | .. | .. | .. | .. | .. |
| | | | | | | | G.M. | 49 | M | A | Neg. | Hypertension | 182/106 | 10/21/47 | 500 | 183/119 | 196/122 | +13/+ 3 | +23/+11 | .. | .. | .. | .. | +13 | .. | .. | .. |
| | | | | | | | * | .. | .. | A | Pos. | Normal | ..... | 10/ 8/47 | 500* | 199/128 | 198/125 | − 1/− 3 | 0/− 2 | .. | .. | .. | .. | | | | |
| A.F. | 39 | M | O | Pos. | Hypertension | Excellent | L.S. | 42 | F | O | Neg. | Hypertension | 205/105 | 8/22/47 | 400 | 158/ 94 | 162/104 | + 4/+10 | +17/+11 | 4 | ‡ | − 6 | ‡ | + 7 | <+14 | +26 | <−25 |
| | | | | | | | N.O. | 36 | M | O | Pos. | Normal | 120/70 | 9/ 5/47 | 300 | 156/ 96 | 160/ 99 | + 4/+ 3 | +10/+ 4 | 4 | + 1 | −32 | +31 | | | | |
| C.O. | 37 | F | A | Pos. | Hypertension | Good | A.K. | 43 | M | A | Neg. | Hypertension | 268/140 | 4/ 7/47 | 200 | 163/110 | ..... | ..... | ..... | 4 | ‡ | − 8 | ‡ | .. | .. | −12 | .. |
| | | | | | | | E.B. | 23 | M | A | Pos. | Normal | 130/70 | 4/ 1/47 | 200 | ..... | ..... | ..... | ..... | 4 | ‡ | + 4 | ‡ | | | | |

†See text under "Results" for method of computing these values.

††Large blood pressure cuff used, 19 cm. in width.

*Venous blood from Blood Bank. Normotensive arterial blood could not be obtained at time of experiment.

**"Neurogenic" classification (9).

‡No pronounced elevation in these values; analytical difficulties preclude presentation of absolute values for mannitol.

<Signifies "less than."

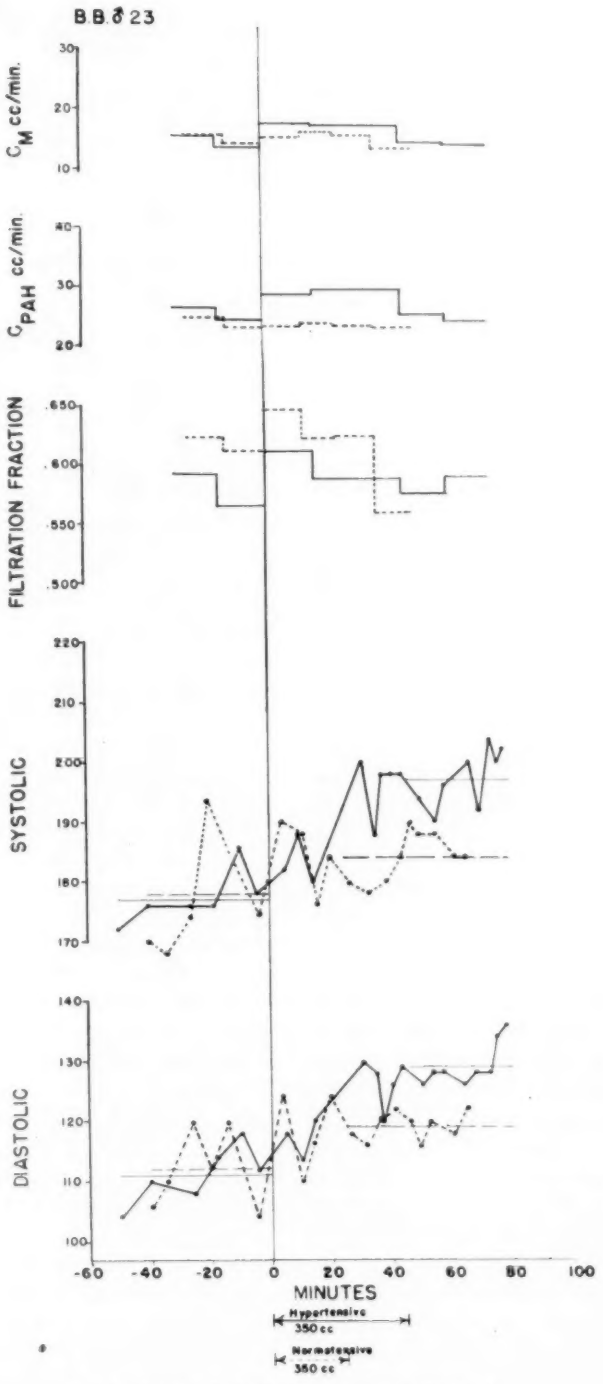


FIG. 3.—Subject B. B. Notations same as Figure 1.

*Venous blood from Blood Bank. Normotensive arterial blood could not be obtained in sufficient quantity.
**"Neurogenic" classification (9).
‡No pronounced elevation in these values; analytical difficulties preclude presentation of absolute values for mannitol.
<Signifies "less than."

motensive blood did occur (Figs 1-3).

Because of the difficulty of interpretation of small changes in very low clearance values, and the probable interrelationship of blood pressure and renal blood flow under these conditions, the data were evaluated by pairs of experiments, comparing the effects of one kind of blood with those produced by the other. In an attempt to ensure that even slight trends would be recognized, the averages of the PAH and mannitol clearances and of the filtration fraction observed during the 2 control periods in each experiment were calculated. Selection was then made of post-transfusion period in which the PAH clearance diverged most markedly from the control average. The extent of the divergence of the clearances and the filtration fraction in this selected period from the appropriate control averages was expressed as percent of the control value (Table I). The percentages thus obtained for the experiments employing normal blood were then subtracted from those obtained in the experiment using hypertensive blood, and the algebraic differences recorded (Table I, last 3 columns).

The data thus expressed in the last 3 columns of Table I permit an analysis of relative changes in PAH clearance in 5 experiments and in mannitol clearance and filtration fraction in 4. Only differences of 15% or more will be given consideration. Relative to the changes produced by normotensive blood, hypertensive blood lowered all 3 values in 1 subject (P. R.). It elevated the mannitol value in another (A. G.). In a third (A. F.) hypertensive blood elevated the PAH clearance and depressed the filtration fraction. The period of greatest change was usually the second period after administration of blood was started.

**Discussion.** In order to demonstrate the presence of pressor substances in the blood of patients with arterial hypertension, at least three avenues of approach might be used to give direct or indirect evidence that such a substance or substances exist. The first might be an increase in blood pressure levels. The second might be reflected in the effect upon renal hemodynamics. The third might be a correlation between renal hemodynamics and blood pressure.

The functional states of the kidneys used in these experiments varied. At first a mild hypertensive was used, C. O., with good renal function, whose blood pressure upon bed rest came down to normal levels. Kidneys in such patients might be sensitive to injected vasoconstrictor substances. No effect upon PAH clearance was noted when hypertensive blood was administered to this patient. In addition, a patient, with sustained, although mild, hypertension, A. F., was studied; his kidneys were apparently normal, as evidenced by a value of 700 cc. per minute for his renal plasma flow and about 115 for his glomerular filtration rate, and a filtration fraction in the neighborhood of .20. Comparison of the effects of transfusion of arterial hypertensive and normotensive blood into this individual revealed relatively less influence of hypertensive blood in elevating the filtration fraction. His diastolic pressure increased slightly after hypertensive blood.

To take the other extreme, kidneys of patients which were poorly functioning might reveal significant changes in the clearance of mannitol and paraamino hippurate, since slight changes in already narrowed arterial beds might be magnified if they occurred. Interpretation of clearance values and decision as to what constitutes a significant change are difficult when severe renal impairment is present. The advanced stages of glomerulonephritis constitute a condition wherein the me-

chanism for the tubular transfer of diodrast is severely damaged, or the loss of renal tubular elements is so great, that the diodrast clearance at low plasma concentrations departs widely from the actual renal plasma flow (3). When experiments on subjects with diminished renal function were done, P. R., A. G., and B. B., the results were not consistent, although changes in the clearances of mannitol, PAH, or in the filtration fractions occurred in 2, P. R. and A. G. The diastolic pressure, however, rose in those two in which these changes were least, A. G. and B. B.

On the basis of these inconsistent results and the variable state of the kidneys of the recipients, it is impossible to ascribe the changes found to the presence in hypertensive blood of substances affecting renal arterioles as measured by clearance methods. On the other hand, the fact that hypertensive blood tended to elevate the blood pressure of the recipients to a greater degree than did normotensive blood is suggestive of the presence of pressor substances. Since the transfusion of hypertensive blood preceded that of normal blood in all instances, except the experiment on H. C., it is possible that the greater pressor effect of the former may have been actually due to the subject's greater apprehension during the initial experiment. The relation between blood pressure changes and those occurring in the kidney could not be correlated in these experiments.

**Summary.** 1. Six hypertensive patients were transfused with arterial hypertensive and later with normotensive blood. The renal plasma flow and glomerular filtration rate were measured in 5, and the blood pressure in 5, before, during and after transfusion.

2. No consistent changes were noted in glomerular filtration, renal plasma flow, or filtration fraction following the transfusions, although in some cases differences did occur.

3. Hypertensive blood tended to elevate the diastolic blood pressure of the recipients to a greater extent than did normotensive blood.

4. These experiments suggest, but do not prove, the presence of pressor substances in the arterial blood of hypertensive individuals.

The authors wish to thank Miss Sallie Wood, R.N., for her valuable assistance in these experiments and Miss Ellabeth Houghton, A.B., and Mrs. Donald Heady for their technical assistance. Mannitol and para-amino hippurate were generously contributed by Sharpe and Dohme.

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# THE INFLUENCE OF ALCOHOL ON THE INTRAVENOUS GALACTOSE TOLERANCE TEST

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Reports concerning the acute effects of ethyl alcohol upon hepatic function have been conflicting.[5,21,28,35,43] However, a number of investigators have indicated that the ability of healthy adults to utilize galactose is impaired by the ingestion of ethyl alcohol.[4,12,34,40,42] The concentration of galactose in the blood, when measured, was found to be abnormally high and the duration of galactosemia abnormally prolonged when the test dose of the sugar was immediately preceded by alcohol. Galactosuria was increased as well. However, the published observations neither establish the minimal effective dose of alcohol nor the duration or site of its action. In only one study[40] was the possibility of altered intestinal absorption of the sugar excluded by its intravenous administration, but the injection was prolonged over a 30 minute period. Therefore, it seemed desirable to define further the influence of alcohol on galactose tolerance.

**Materials, Experimental Procedure, and Methods.** A total of 46 intravenous galactose tolerance tests were performed on 19 individuals including 15 healthy adults, 2 patients with cirrhosis, 1 with hyperthyroidism, and 1 with psychoneurosis. The subjects were allowed water, but not food, during an overnight fast and were kept at bed rest or restricted activity. Each one voided immediately beforehand, and then had his urine collected during the experimental period. Galactose was administered intravenously, as a 50% solution in distilled water. Dosages of 0.4, 0.5, and 0.6 gm. per kg. of body weight were employed and the injections were completed within 3 to 7 minutes. Venous blood was obtained immediately before the injection and at 15, 45, and 75 minutes after its mid-point. Samples (2.0 ml.) of the oxalated whole blood were fermented to remove glucose by continuous shaking with 6 cc. of 20% bakers' yeast for 30 minutes at room temperature. Deproteinization was then accomplished by the addition of zinc sulfate and sodium hydroxide.[38] Aliquots (5.0 ml.) of the blood filtrates (corresponding to 0.4 ml. of whole blood) were analyzed in duplicate for galactose by the iodimetric method of Somogyi, as were the urine samples.[39] Recoveries of known amounts of galactose added to oxalated whole blood were complete and were not altered by addition of ethyl alcohol to the blood *in vitro* or when the blood donor had ingested alcohol.** Moreover, alcohol did not increase the concentration of non-glucose reducing substances in the blood blanks.

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** Non-fermentable reducing substance was detectable in the fasting blood samples in only 8 of the 46 tests at concentrations of 4 to 19 mg. per 100 cc. In these 8 tests galactose concentrations were calculated at the difference between total non-glucose reducing substance and the observed "blood blank."

The response of 10 of the subjects to a standard dose of galactose administered intravenously was first established in one or more studies. Subsequently, the effect of ethyl alcohol ingestion on the blood galactose levels and on the excretion of this sugar in urine during an otherwise identical test was determined. A single dose of 95% ethyl alcohol in amounts of 0.03 to 0.40 cc. per kg. of body weight was given in 100 cc. of water at an interval which varied from 15 minutes to 24 hours before the administration of the sugar. To test the specificity of the influence of alcohol on galactose tolerance, levulose tolerance tests[7,8,38,39] and glucose tolerance tests[7,27,38,39] were performed in 8 experiments with, and 6 without, preliminary administration of ethyl alcohol in doses of 0.30 cc. per kg. In 6 subjects, the rate of removal of bromsulfalein from the serum was measured with and without previous ingestion of alcohol.[36]

**Results.** *Galactose Tolerance* (Table 1). The control galactose tests of the healthy subjeects are in approximate agreement with previously reported normal values.[1,2,3,13,18,22,24,37]§ One subject (B.J.K.) received 0.4 gm. of galactose per kg. of body weight on one occasion and 0.6 gm. per kg. at another time. The blood levels at each point in the curve were distinctly lower following the smaller dose. The levels observed in the group of 5 subjects receiving 0.5 gm. per kg. were not apparently different at any time interval from those found in the group of 5 given 0.6 gm. per kg. The patient with hyperthyroidism had a normal galactose tolerance test (Table 1), whereas the 2 subjects with cirrhosis of the liver had impaired tolerances (Table 3). The small magnitude of variations in repeated tolerance tests carried out under standard conditions in the same subject is evident from the results of the 2 studies performed 6 weeks apart on J.R. and the 5 on J.T. during one month (Tables 1 and 2).

*Effect of alcohol on the galactose tolerance* (Table 2). The galactose tolerance test was significantly altered in all 10 subjects without liver disease when 0.26 to 0.40 cc. of ethyl alcohol per kg. of body weight was ingested 15 minutes before the injection of the sugar. The decreased rate of removal was most evident in increased galactosemia at 45 and 75 minutes, although higher blood levels were sometimes observed at 15 minutes. An increase in

TABLE 1.—INTRAVENOUS GALACTOSE TOLERANCE TESTS IN HEALTHY ADULTS

| | Galactose Injected (gm. per kg.) | Age (years) | Sex | Body Weight (kg.) | Blood galactose (mg. per 100 cc.)* Time (minutes) 15 | 45 | 75 | Excretion in 75 minutes Urine (cc.) | Galactose (gm.) |
|---|---|---|---|---|---|---|---|---|---|
| LG | 0.6 | 27 | M | 68 | 125 | 27† | 12 | 100 | 4.6 |
| JCR | 0.6 | 33 | M | 70 | 150 | 30 | 10 | 103 | 3.5 |
| JP | 0.6 | 31 | M | 66 | 171 | 76 | 10 | 137 | 5.5 |
| JM | 0.6 | 19 | F | 57 | 209 | 72 | 12 | — | — |
| BJK(a) | 0.6 | 22 | F | 60 | 191 | 74 | 18 | 103 | 4.3 |
| JR (a) | 0.5 | 34 | M | 65 | 157 | 30 | 11 | 195 | 2.1 |
| JR (b) | 0.5 | 34 | M | 65 | 147 | 25 | 14 | — | — |
| JT | 0.5 | 31 | M | 77 | 147 | 56 | 16 | 114 | 5.4 |
| FM | 0.5 | 27 | M | 63 | 152 | 50 | 16 | 75 | 4.8 |
| DG | 0.5 | 23 | F | 52 | 131 | 7 | 3 | 83 | 1.9 |
| MC‡ | 0.5 | 27 | F | 50 | 167 | 57 | 11 | 205 | 2.2 |
| BJK(b) | 0.4 | 22 | F | 60 | 86 | 18 | 6 | 78 | 2.0 |

* Values for blood galactose at 15, 45, and 75 minutes are corrected for blood blanks.
† = 49 minutes.
‡ = Hyperthyroid.

§ The analytical method used in the present study permitted determination of blood galactose in concentrations as low as 5 mg. per 100 cc. Galactose has invariably been found in the blood at 75 minutes in concentration of less than 21 mg. per 100 cc. Investigators who report complete removal of galactose from the blood 75 minutes after its intravenous administration in comparable dosage,[3,18,22] have employed analytical methods which are less sensitive at low levels.

the urinary excretion of galactose was also apparent in most instances, but the degree of galactosuria in control tests had been quite variable. Significant galactosemia persisted for at least 120 minutes in the one subject (L.G.) whose blood level was determined after this time interval. In addition, alcohol in the same dosage produced a delay in galactose removal from the blood on the 4 occasions when it was taken 1.0 to 1.25 hours before the sugar. No alteration of the galactose tolerance curve was noted in the 2 experiments in which the interval between alcohol and galactose administration was extended to 2 hours, nor was any effect apparent in 7 other studies carried out 3, 6, 12, and 24 hours after alcohol ingestion. Less marked but still definitive alteration of the tolerance test was observed when 0.16 to 0.20 cc. of alcohol per kg. was ingested 15 minutes before the test in 3 experiments. Doses of 0.13 cc. per kg. or less in 4 tests had no demonstrable effect on the blood levels.

The results recorded in Table 3 indicate that alcohol produced no definitive evidence of further impair-

TABLE 2.—INTRAVENOUS GALACTOSE TOLERANCE TESTS FOLLOWING THE INGESTION OF ALCOHOL

| | Age | Sex | Body Weight (kg.) | Interval between alcohol & galactose (hours) | Dosage of alcohol (cc./kg.) | Blood galactose (mg. per 100 cc.) Time (minutes) 15 | 45 | 75 | Excretion in 75 minutes Urine (cc.) | Galactose (gm.) |
|---|---|---|---|---|---|---|---|---|---|---|
| JCR | 33 | M | 70 | 0.25 | 0.03 | 176 | 54 | 23 | 178 | 16.2 |
| JT | 31 | M | 77 | 0.25 | 0.06 | 123 | 35 | 9 | 96 | 5.7 |
| FM | 27 | M | 63 | 0.25 | 0.10 | — | — | 10 | 96 | 4.2 |
| JT | 31 | M | 77 | 0.25 | 0.13 | 157 | — | 17 | 224 | 12.3 |
| CM | 15 | M | 61 | 0.25 | 0.16 | 141 | 75 | 31 | 212 | 14.7 |
| LF | 35 | F | 50 | 0.25 | 0.20 | 162 | 94 | 37 | 125 | 8.7 |
| AS | 64 | M | 54 | 0.25 | 0.20 | — | — | 32 | 121 | 2.9 |
| JT | 31 | M | 77 | 0.25 | 0.26 | 179 | 106 | 74 | 264 | 8.8 |
| JM* | 19 | F | 57 | 0.25 | 0.26 | 184 | 134 | 85 | 157 | 2.2 |
| LG* | 27 | M | 68 | 0.25 | 0.29 | 152 | 94 | 65** | 363 | 7.6 |
| JCR* | 33 | M | 70 | 0.25 | 0.29 | 195 | 111 | 59 | 180 | 8.7 |
| JR | 34 | M | 65 | 0.25 | 0.30 | 168 | 103 | 67 | 620 | 12.0 |
| RO | 23 | F | 60 | 0.25 | 0.33 | — | — | 75 | 190 | 6.2 |
| BJK | 22 | F | 60 | 0.25 | 0.33 | 182 | 121 | 82 | 125 | 2.2 |
| AB§ | 15 | F | 55 | 0.25 | 0.36 | 161 | — | 60 | 68 | 3.9 |
| IL | 24 | F | 54 | 0.25 | 0.37 | 156 | — | 68 | 162 | 2.7 |
| MC† | 27 | F | 50 | 0.25 | 0.40 | 163 | — | 54 | 430 | 4.1 |
| JT | 31 | M | 77 | 1.00 | 0.30 | — | — | 77 | 230 | 6.6 |
| FM | 27 | M | 63 | 1.00 | 0.30 | — | — | 68 | 256 | 7.4 |
| RO | 23 | F | 60 | 1.17 | 0.33 | 172 | — | 26 | 139 | 6.3 |
| JT | 31 | M | 77 | 1.25 | 0.26 | — | — | 39 | 114 | 5.3 |
| LT | 59 | F | 44 | 2.00 | 0.30 | — | — | 8 | 146 | 1.8 |
| AS | 64 | M | 54 | 2.00 | 0.30 | — | — | 20 | 143 | 2.3 |
| RO | 23 | F | 60 | 3.00 | 0.33 | 196 | — | 15 | 90 | 7.0 |
| JT | 31 | M | 77 | 6.00 | 0.26 | 180 | 76 | 18 | 96 | 5.6 |
| JT | 31 | M | 77 | 12.00 | 0.26 | 175 | 52 | 11 | 77 | 3.9 |
| RO | 23 | F | 60 | 12.00 | 0.33 | 175 | 79 | 20 | 124 | 4.2 |
| JT | 31 | M | 77 | 24.00 | 0.26 | 155 | 53 | 15 | 122 | 5.6 |
| IL | 24 | F | 54 | 24.00 | 0.37 | 150 | — | 19 | 81 | 2.2 |
| LF | 35 | F | 50 | 24.00 | 0.40 | 120‡ | — | 12‡ | 123 | 0.5 |

* These 3 subjects received 0.6 gm. galactose per kg. of body weight. All others were given 0.5 gm. per kg.
** Decreased to 39 mg. per 100 cc. at 120 minutes.
§ Psychoneurosis.
† Hyperthyroidism.
‡ Blood taken at 20 and at 80 minutes respectively.

ment of galactose tolerance in the 2 patients with cirrhosis of the liver.

The administration of alcohol had no discernible effect on the utilization of glucose or levulose nor did it change the fasting blood sugar (Table 4). Neither did the alcohol alter the bromsulfalein excretion rate in the 6 subjects tested. Thirty minutes after the intravenous administration of 5 mg. per kg. of body weight, less than 10 mg. per 100 cc. of the dye was detectable in the serum of the healthy subjects. Similarly the 2 patients with cirrhosis of the liver exhibited no further impairment of their already diminished capacity to excrete the substance. These data have not been tabulated.

**Discussion.** The results demonstrate clearly that small amounts of ethyl alcohol produce significant and consistent abnormalities of the galactose tolerance test in healthy adults. Blood levels of galactose at 75 minutes increased in some instances as much as 5-fold following alcohol ingestion, and distinct elevations were also observed at 45 minutes. The 15 minute values showed less consistent changes, presumably because these were in part determined by the speed of injection and the rate of diffusion through the body fluids. Slight delay in galactose removal was observed when alcohol was taken in quantities as small as 0.16 cc. per kg. of body weight. Stentsam[40] has reported increased galactosemia in one healthy subject who received as little as .03 or .08 cc.

TABLE 3.—INTRAVENOUS GALACTOSE TOLERANCE TESTS WITH AND WITHOUT PRELIMINARY ALCOHOL INGESTION IN SUBJECTS WITH CIRRHOSIS OF THE LIVER.

| | Age | Sex | Body Weight (kg.) | Dosage of alcohol* (cc./kg.) | Blood galactose (mg. per 100 cc.) Time (minutes) 15 | 45 | 75 | Excretion in 75 minutes Urine (cc.) | Galactose (gm.) |
|---|---|---|---|---|---|---|---|---|---|
| JC (a) | 50 | M | 66 | 0 | 144 | 84 | 42 | 154 | 1.8 |
| LB (a) | 48 | M | 78 | 0 | 159 | — | 88 | 210 | 3.6 |
| JC (b) | 50 | M | 66 | 0.3 | 165 | — | 44 | 210 | 2.7 |
| LB (b) | 48 | M | 78 | 0.3 | 157 | — | 82 | 83 | 2.5 |

* Given 15 minutes before galactose.

TABLE 4.—GLUCOSE AND LEVULOSE TOLERANCE TESTS WITH AND WITHOUT PRELIMINARY INGESTION OF ALCOHOL.

| Subject | Age | Sex | Body Weight (kg.) | Dosage of alcohol* (cc./kg.) | Blood sugar (mg. per 100 cc.) Time (minutes) 0 | 30 | 60 | 90 | 120 |
|---|---|---|---|---|---|---|---|---|---|
| A. Glucose 25 gm. intravenously | | | | | | | | | |
| JR | 34 | M | 65 | 0 | 79 | — | — | — | 73 |
| | | | | 0.3 | 84 | — | — | — | 67 |
| AA | 29 | M | 60 | 0 | 75 | — | — | — | 72 |
| | | | | 0.3 | 81 | — | — | — | 57 |
| TZ | 26 | M | 70 | 0 | 89 | — | — | — | 91 |
| | | | | 0.3 | 88 | — | — | — | 75 |
| AO | 50 | F | 60 | 0.3 | 87 | — | 135 | — | 74 |
| B. Levulose 40 gm. orally | | | | | | | | | |
| JR | 34 | M | 65 | 0 | 90 | 126 | 130 | 71 | 77 |
| | | | | 0.3 | 88 | 120 | 126 | 82 | 70 |
| GM | 60 | M | 95 | 0 | 80 | 102 | 86 | 77 | 82 |
| | | | | 0.3 | 82 | 102 | 93 | 66 | 69 |
| AD | 24 | M | 90 | 0 | 73 | 86 | 86 | 77 | 75 |
| | | | | 0.3 | 73 | 95 | 90 | 65 | 54 |
| IL | 24 | F | 54 | 0.3 | 86 | 105 | 105 | 78 | 77 |

* Given 15 minutes before administration of sugar.

of alcohol per kg., but only small doses of galactose were given and the sugar was taken by mouth.

In the present study the degree of abnormality of the tolerance test was proportional to the dose of alcohol over the low dosage range studies. Moreover, the abnormality was demonstrable for a relatively short time after alcohol ingestion. This would be anticipated if the effect of alcohol on galactose removal was dependent on the blood alcohol concentration during the test.[11] It seems probable that doses of alcohol larger than 0.4 cc. per kg. of body weight might well alter the galactose tolerance test for longer periods. Indeed, suggestive confirmation of this possibility has been obtained in one subject who displayed an abnormal tolerance test 60 hours after a very large, but unmeasured, intake of alcohol.

It is apparent that the elevated concentrations of galactose in the blood following ethyl alcohol ingestion were the results of retarded removal of the sugar from the blood stream, since it was administered by the intravenous route, and urinary excretion usually accounts for only a small fraction of the galactose leaving the circulation in man. In these experiments, the increased galactosuria noted after alcohol proved that elevation and prolongation of galactosemia could not be related to decreased renal excretion of the sugar. Since the analytical method for galactose actually measured the total concentration of unfermentable reducing substances in the blood filtrate, the possibility that some other non-fermentable reducing compound enters the blood stream while galactose is being removed at a normal rate might be considered. However, the failure of such a substance to appear in the blood when alcohol alone is given and the normal glucose and levulose tolerance tests after alcohol ingestion eliminate such an hypothesis from serious consideration. It is reasonable to assume that the removal of galactose is delayed because of interference with its uptake and conversion to glycogen by the liver. In the hepatectomized dog, galactose cannot be utilized as a source of blood glucose and the rate of galactose removal from the blood is extremely slow if renal excretion is prevented.[9] All the available evidence derived from animal experimentation points to the dominant role of the liver in galactose utilization.[16,17] Clinical observations indicate that only in hepatic disease is the intravenous galactose tolerance test significantly altered.[1,2,3,13,18,22,24,37] No differences have been detected between the persistently abnormal galactose tolerance test of patients with liver disease and the transiently impaired curves of normal subjects given alcohol. The failure of alcohol further to impair the galactose tolerance in patients with hepatic disease[4,34,40] lends additional support to the view that the liver is the site of the alcohol action.

Although the argument is strong that alcohol influences galactose removal by impairing hepatic uptake, and presumably the conversion of galactose to glycogen, there is little support for the view that any general impairment of liver function is produced by the doses employed. Indeed, the failure of alcohol to decrease levulose tolerance suggests a highly specific action of alcohol on the hepatic enzyme systems involved in handling galactose.* Moreover, no impairment of bromsulfalein excretion was demonstrated in the present study. MacNider[28] observed temporary impairment of phenoltetrachlorphthalein excretion in dogs poisoned with large

* Recently, the identification of an enzyme, "galactokinase", which catalyzes the conversion of galactose to galactose-1-phosphate by the yeast *Saccharomyces fragilis* has been reported.[41] It is of interest that one of the characteristic properties of this enzyme is that its activity is easily impaired by treatment with alcohol.

doses of ethyl alcohol, 10 to 15 cc. of a 40% solution per kg., repeated as required to maintain a state of seminarcosis for 12 to 24 hours. Rosenthal[35] gave dogs smaller doses of ethyl alcohol (2 cc. of a 98% solution per kg.) and found normal concentrations of urine urobilinogen and serum bilirubin with only a slight delay in bromsulfalein excretion 2 to 6 hours later. In proportion to body weight, the dose employed by Rosenthal is almost 7 times as large as the quantity required to produce marked impairment of galactose tolerance in man. Little has been published concerning the immediate effects of alcohol on other tests of liver function in human subjects. The few available reports[5,21,43] deal with observations made after, but not during, an episode of acute alcoholism. The problem deserves further investigation with the aid of modern sensitive methods.[44] However, it seems clear that the ability of the liver to handle galactose is peculiarly susceptible to impairment by alcohol. The observation that alcohol interferes with the removal of galactose from the blood is of practical importance in the interpretation of galactose tolerance tests used in the evaluation of hepatic function or designed to reflect rates of intestinal absorption.[2] It is of even greater theoretical interest with respect to the well recognized clinical association between alcoholism and portal cirrhosis of the liver[14,19,23,31,33] and the possible role of alcohol in the pathogenesis of this disease.[6,14,15,25,26,31] Finally, it has been suggested,[16,29,30,32] on the basis of studies concerning infants with chronic galactosemia, that the continued failure properly to utilize galactose derived from the diet may of itself lead to hepatic damage. Further evidence in support of this hypothesis has been presented elsewhere.[20]

**Summary.** Ethyl alcohol in small doses temporarily reduced the galactose tolerance of healthy adults, but did not influence the already abnormal tolerance tests of 2 patients with cirrhosis of the liver.

Although the abnormal tests following alcohol ingestion were almost certainly due to impairment of the ability of the liver to remove galactose from the blood stream, there was no concomitant impairment of bromsulfalein excretion or of levulose and glucose tolerance.

The significance of these findings is discussed.

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# CERTAIN EFFECTS OF SALT POOR HUMAN ALBUMIN IN CASES OF HEPATIC DISEASE*

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Recent studies[1,7,9,12,16] have indicated considerable doubt about the benefit to be expected from human albumin therapy in cases of cirrhosis of the liver. In some instances good results were noted in the treatment of ascites, especially if the patients were tapped dry before administration of the albumin.[1]

We have been interested in following the effects of considerable amounts of salt poor human albumin in cases of liver disease of various types. In previous reports little mention has been made of untoward effects. We have been impressed in particular by an unfavorable water retention in some cases, often associated with fever and pulmonary edema. The purpose of the present communication is to describe our observation in these cases and at the same time make some comment on the value of salt poor human albumin in the treatment of liver disease.

**Material and Methods.** Salt poor human albumin has been administered to a number of patients suffering from various types of hepatic disease, on the Medical Service of the University of Minnesota Hospital. Six of these have been studied in more detail and form the material for the present communication. Two of the 6 were chronic alcoholics and were suffering from so-called alcoholic cirrhosis of the liver; three had cirrhosis believed to be a sequel of sporadic infectious hepatitis, and one had homologous serum hepatitis.

The following studies were carried out: Serum bilirubin,[3] urine urobilinogen,[15] feces urobilinogen,[15] cephalin cholesterol,[5] thymol turbidity,[10] serum cholesterol and cholesterol esters.[14]

The salt poor human albumin was provided through the courtesy of the American National Red Cross in a 25% solution, the solvent consisting of a 0.3 M sodium chloride solution. The desired amount of albumin, ranging from 25 to 100 gm. per injection, was diluted with 500 to 1000 cc. of 5% dextrose in distilled water and administered intravenously at the rate of about 250 cc. per hour.

Liver biopsy under peritoneoscopic control was performed as previously described.[6]

The "liver diet" which will be referred to consists of 350 gm. of carbohydrate, 150 gm. protein, and 100 gm. of fat per day.

**Protocols.** Case 1. E. R., a 64 year old white male undertaker, entered the hospital on Oct. 24, 1947. He complained of pruritus, anorexia, nausea, jaundice and light colored stools for the previous 2 weeks. A malignant melanoma had been removed 2 years before. A mesonephric ridge tumor was removed in May, 1947, at which time he had been given 14 blood transfusions. Physical examination revealed icteric sclerae, multiple petechiae, foetor hepaticus, and hepatomegaly to the level of the umbilicus. The spleen was palpable 1 inch below the left costal margin. The liver function studies are shown in Fig. 1. On Oct. 24 he was placed on a liver diet, multivitamins, and high caloric feedings. Increasing jaundice, anorexia and diminution of the size of the liver developed. The patient was somnolent and foetor hepaticus was pronounced. Six hundred gm. of salt poor human albumin were given between Nov. 7 and 12, incl. During this period the patient began to improve and went on to rapid and evidently complete recovery. At first this was attributed

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to the apparent effect of the serum albumin. Though the patient did not appear to improve until the third day of albumin therapy, the attending physician felt convinced of its value; in fact he regarded it as little short of life saving. Nevertheless, it is seen in Fig. 1, that there was a significant decrease in the serum bilirubin just prior to the beginning of albumin therapy, so that the question of coincidental spontaneous recovery is obvious. No untoward effects of the albumin were noted in this case.

CASE 2. O. S., a 42 year old white housewife and tavern operator, was admitted on January 13, 1948. She complained of vomiting and jaundice for 6 weeks prior to admission. A history was obtained of poor appetite, low protein intake, and alcohol ingestion for 6 years previous to entry. Spider naevi, ascites, and moderate edema of the lower extremities were noted on physical examination. The liver was enlarged to 10 cm. below the right costal margin in the midclavicular line. For the first 13 days she was treated with a liver diet supplemented with an enriched milk mixture.* No significant improvement was noted. From Jan. 26, 1948, to Feb. 4, 1948, inclusive, salt poor human albumin was administered daily to a total of 950 gm. The effect on the serum albumin, serum globulin, and other observations are shown in Fig. 2. Of particular interest is the reversal of the albulin-globulin ratio and the marked decline of the thymol turbidity, without change in the cephalin flocculation. No diuresis was observed; in fact, the urine volume diminished somewhat, and the patient gained weight. A liver biopsy at this time revealed a severe fatty cirrhosis with considerable degenerative change represented by open spaces.** There was increasing evidence of hepatic insufficiency. Somnolence, intermittent foetor hepaticus, and increasing peripheral edema were observed. From Feb. 5th to Feb. 28th, 1500 cc. of 20% glucose containing 75 units of insulin were administered daily. From Feb. 11 to Feb. 28, 10 cc. of intraheptol were also administered daily. Definite improvement had already begun, however, on Feb. 11th. This was ushered in with a con-

TABLE 1.—OBSERVATIONS IN CASE 3 (T. C.)

| Observation or material given | Day of Study – May, 1948 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| Salt Poor Human Albumin, Grams (Intravenous) | | | | | | 50 | 100 | 100 | 100 | 100 | 100 | | | |
| 5% Glucose in Distilled Water (Liters) | | | | | | 0.5 | 1.0 | 0.8 | 0.8 | 0.6 | 0.8 | | | |
| Weight (lbs.) | | 144 | 143 | 142 | 144 | 141 | 143 | 143 | 144 | | 149 | 151 | | Died |
| Urine Volume (L.) | 1.9 | 2.0 | 2.8 | 2.2 | 2.5 | 1.1 | 3.0 | 2.0 | | 2.1 | 1.0 | 0.9 | | |
| Bilirubin (mg./100cc.) | | | | | | | | | | | | | | |
| One Minute | | 1.8 | | | | 2.1 | | | 1.6 | | 1.5 | | 2.4 | |
| Total | | 3.8 | | | | 4.6 | | | 2.3 | | 4.9 | | 7.9 | |
| Cephalin Cholesterol (24 and 48 hr.) | | 3+4+ | | | | | | | 3+4+ | | 3+4+ | | 3+4+ | |
| Thymol Turbidity (Units) | | 7.8 | | | | 10.8 | | | 5.5 | | 5.5 | | 5.5 | |
| Alkaline Phosphatase (Bodansky units) | | 6.1 | | | | 5.9 | | | 5.3 | | 3.8 | | | |
| Cholesterol (mg. per 100 cc.) | | | | | | | | | | | | | | |
| Total | | 146 | | | | 160 | | | 110 | | 130 | | 72 | |
| Esters | | 57 | | | | 83 | | | 57 | | 95 | | 28 | |
| Serum Proteins Gm./100 cc. | | | | | | | | | | | | | | |
| Albumin | | | | | | 2.7 | | | 4.8 | | 5.3 | | 5.3 | |
| Globulin | | | | | | 4.8 | | | 3.2 | | 2.9 | | 3.3 | |

* Milk 6-8: Meritene 1. The latter is a dehydrated milk-calcium caseinate-lactose powder provided through the courtesy of the Dietene Corporation, Minneapolis, Minn.

** Photomicrographs are reproduced elsewhere.[17]

siderable diuresis, followed by improved appetite, mental clarity and diminishing jaundice. Over a period of 2 months the jaundice entirely disappeared. At the present time the patient feels very well. This case was instructive because of the obvious water retention and gain in weight in spite of elevation of the serum albumin to 5.0 gm. per 100 cc. This was associated with deterioration of her general status, rapid improvement occurring, however, upon administration of hypertonic glucose solution.

Case 3. T. C., a 41 year old white road construction laborer, entered the hospital on March 15, 1948. Two years previously, in March, 1946, he had noted dark urine, weakness, and anorexia. In April 1946 an appendectomy was performed. In June 1946, jaundice, anorexia, dark urine, and weakness developed. These recurred in February 1947 and again in June 1947. He was first seen in the University Hospital in August 1947. At that time, a liver biopsy revealed portal cirrhosis. He improved somewhat, was discharged on August 15 and felt fairly well until November 1947 when his symptoms recurred, and steadily increased in severity. On admission, the significant physical findings were lethargy, palmar erythema, spider nevi, ascites, splenomegaly, and an enlarged firm liver. From March 23 to May 7 he received the liver diet, enriched milk mixture, and 10 cc. daily of intraheptol. No significant improvement was observed. From May 7 to May 12 he was given a total of 550 gm. of salt poor human albumin. On May 11 he complained of a severe headache and a feeling of tiredness. He appeared quite lethargic. On May 12th, moist râles were noted at the lung bases. Fever up to 102° was noted on May 13th. On the same day a severe nose bleed occurred. He was apprehensive and sweating profusely. Dyspnea was observed the following day and his venous pressure was 17 cm. On May 14th his blood volume was 6.85 liters as compared to a statistical normal of 5.6 liters (Evans blue dye method). The hematocrit was 33.6%, plasma volume 4.46 liters.

Early in the afternoon of the 14th, 600 cc. of blood was removed, following which the patient felt considerably improved. About midnight, however, he became much more dyspneic, and died rather suddenly at 12:15 A.M. The significant findings at necropsy were as follows: Pulmonary congestion and edema, bilateral pleural effusion, ascites, and a diffuse, non fatty cirrhosis of the liver. The latter was classified as probably post infectious in character. The significant laboratory data in Case 3 are given in Table 1.

Again it is clear that there was marked water retention as a result of the albumin therapy with gain in weight and severe pulmonary edema in spite of an elevation of the serum albumin to 5.3 gm. per 100 cc. In retrospect it seems possible that the fatal outcome might have been avoided if plasma-

TABLE 2.—LIVER FUNCTION STUDIES BEFORE AND AFTER THE ADMINISTRATION OF SALT POOR HUMAN ALBUMIN, IN CASES 4, 5 AND 6

| Observation | Case 4, H. A. | | | | Case 5, C. A. | | | Case 6, D. M. | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | | | Before | After | | Before | After | |
| | 2-9-48 | 2-16-48 | 2-27-48 | 3-5-48 | 4-19-48 | 4-30-48 | 5-8-48 | 2-11-48 | 2-18-48 | 3-1-48 |
| Cephalin Cholesterol (24 and 48 hr.) | 3+4+ | 3+4+ | | 3+4+ | 3+4+ | 3+3+ | | 3+4+ | 3+4+ | 3+4+ |
| Thymol Turbidity (units) | 2.9 | 1.7 | | 3.6 | 6.5 | 3.9 | | 9.2 | 5.5 | 7.8 |
| Serum Bilirubin | | | | | | | | | | |
| One Minute | 1.0 | 1.0 | | 0.6 | 2.4 | 2.1 | patient | 12.5 | 11.2 | 9.3 |
| Total (mg./100 cc.) | 3.5 | 3.6 | | 3.5 | 4.9 | 4.2 | died | 23.5 | 21.5 | 15.6 |
| Serum Protein (Gm./100 cc.) | | | | | | | | | | |
| Albumin | 2.8 | 3.9 | 3.2 | | 1.2 | 2.2 | | 2.7 | 5.3 | 4.3 |
| Globulin | 3.7 | 2.1 | 3.1 | | 5.8 | 4.3 | | 4.2 | 2.7 | 3.1 |
| Cholesterol (Mg./100 cc.) | | | | | | | | | | |
| Total | 140 | 66 | | 98 | 56 | 36 | | 106 | 56 | 72 |
| Esters | 90 | 33 | | 50 | 7 | 9 | | 29 | 21 | 14 |
| Alkaline Phosphatase (Bodansky units) | 6.1 | 2.8 | | 5.0 | 1.5 | 1.4 | | 16 | 5.0 | 8.1 |

phoresis had been done when the magnitude of increase of the plasma volume was learned. Unfortunately there was so much apparent improvement following the removal of 600 cc. of blood, that a sense of false security was gained.

CASE 4. H. A., a 56 year old white liquor salesman entered the hospital on Jan. 31, 1948. He complained of jaundice and intermittent dark urine. For 2 years prior to admission he had noted transient jaundice and ankle edema. A mild psychic disturbance was noted in Oct. 1947. Several paracenteses had been performed a few months prior to admission. A long history of alcoholism was obtained. Physical examination revealed icteric sclerae, spider nevi, foetor hepaticus, and ascites. The liver was not palpable. Liver function studies are shown in Table 2. The liver biopsy on Feb. 6, 1948, revealed extensive portal cirrhosis. From Feb. 8, 1948, to Feb. 14, 1948, he was given 700 gm. of salt poor albumin in dosages of 100 gm. daily. After the first 200 gm. had been given fever up to 103° was noted every day until Feb. 22. No diuresis was observed. His face was suffused and his skin red. A chest film on May 14th revealed congestion of the lungs and a suggestion of infiltration in the lower portion of the left lung. The changes in liver function were not remarkable (Table 2).

CASE 5. C. A., a 68 year old white housewife, entered the hospital on Feb. 22, 1948. For the previous 2 months she had noted weakness, anorexia, nausea, vomiting, jaundice, and pruritus. She stated that her stools had been light and her urine dark. Diabetes mellitus had been diagnosed by her physician one month before admission. There had been a 40 pound weight loss in the last 4 months, most of which had occurred in the previous 2 months. Physical examination revealed a beefy red tongue and icteric sclerae. The liver was not palpable. Pretibial edema of a mild degree was present. Liver biopsy revealed marked evidence of hepatitis and cirrhosis. Her liver function studies are shown in Table 2. From Feb. 22, 1948, to March 13, 1948, she was given a liver diet supplemented with intravenous and oral glucose. From March 13 to April 19 an enriched milk mixture was added to this regime. No significant improvement was observed and ascites developed.

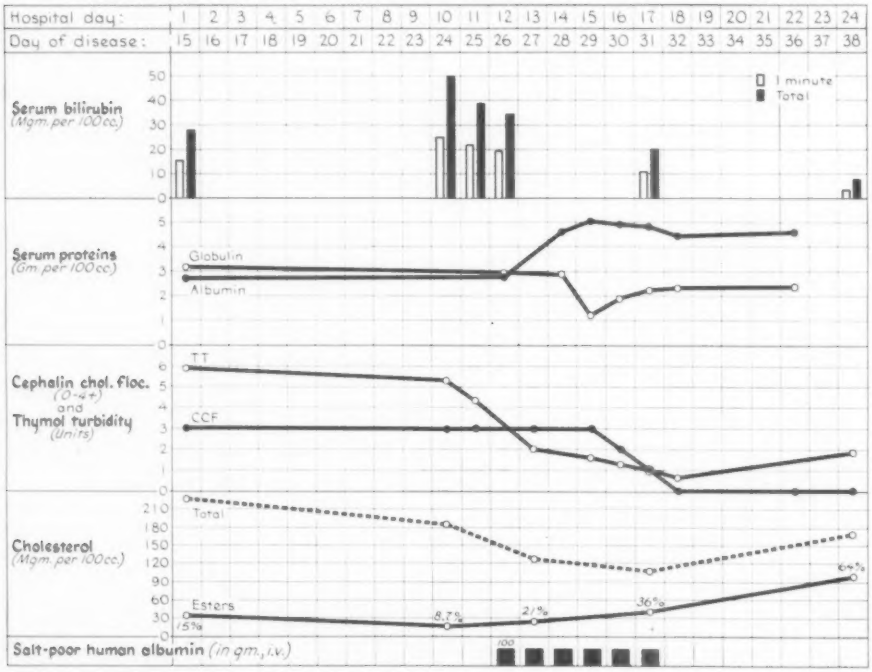


FIG. 1.—Serial liver function studies in Case 1, before and after administration of salt poor human albumin (E. R., male, age 64).

From April 19 to April 30, 1948, a total of 300 gm. of salt poor human albumin was administered. Fever was noted following each injection. Dyspnea was also observed after the last several injections. No diuresis occurred. The patient's condition became progressively worse. She expired on May 8, 1948. The various features of this case were similar in many respects to those recently studied in Denmark.[8,11]

Case 6. D. M., a 33 year old white male school teacher, was admitted to the hospital on Feb. 3, 1948. He complained of jaundice, dark urine, light stools, ankle edema, and bleeding from the gums. He had first noticed these symptoms in March, 1947. At that time he had lost about 25 pounds in weight. After about 3 months the jaundice almost disappeared and he felt fairly well except that he did not regain the weight he had lost nor did he regain his usual vigor. In November, 1947, his symptoms recurred and became progressively worse until the time of admission. Physical examination revealed intense icterus, numerous excoriations, spider nevi, and ankle edema. His liver was palpable 12 cm. below the right costal margin. A liver biopsy revealed hepatitis and distinct, early cirrhosis. From Feb. 10 to Feb. 18, 1948, he was given 1000 gm. of salt poor albumin intravenously. During this time he showed no significant changes in his liver function studies. No diuresis was observed. Fever up to 103.6° was noted during the administration of the albumin. His respiratory rate was increased. No immediate beneficial effect was observed from this therapy. Table 2 includes a summary of his liver function studies prior to and after the administration of salt poor human albumin. About 2 months later the jaundice commenced to lessen and by the first of June, 1948, had entirely disappeared. The patient now feels quite well and has resumed his occupation.

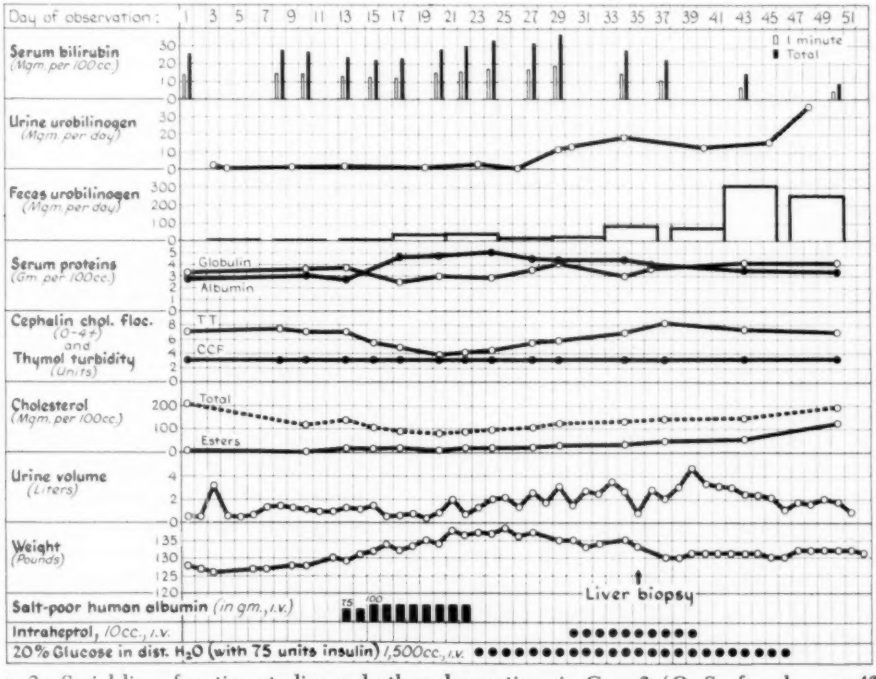


Fig. 2.—Serial liver function studies and other observations in Case 2 (O. S., female, age 42).

**Comment.** The above cases fail to prove any significant value of salt poor human albumin in cases of hepatitis and, or, cirrhosis. On the other hand, the possibility exists that the material may be of considerable value in certain cases. This is at least suggested in Cases 1 and 2 of the present group. In the former, however, there is a likeli-

hood of a coincidental, spontaneous improvement, and in the latter, the improvement, while dramatic and following shortly upon the albumin therapy, did not begin until hypertonic glucose had been administered in considerable amount. One must consider the possibility in this instance that the latter would not have been helpful without the previous replenishment of nitrogen which the albumin undoubtedly effected. It is also possible that the improvement was entirely due to the albumin, as evidence of delayed benefit has been reported previously.[4,9] Thus Eckhardt and co-workers[4] have shown that albumin given intravenously in normal human subjects is rather slowly but completely metabolized, giving rise to a markedly positive nitrogen balance.

While the present study thus fails to decide as to the value of salt poor albumin in the treatment of liver disease, it emphasizes certain dangers attendant on its use and is instructive with respect to certain aspects of renal function in cases of cirrhosis.

It is quite clear from the present cases, that fever and retention of water may be anticipated when salt poor human albumin is given to patients with cirrhosis in the amounts which have been thought to be necessary.[9] The administration of salt poor human albumin has recently been shown by Cargill[2] to increase glomerular filtration and renal blood flow in normal and nephrotic individuals. Cases of hepatic disease were not included. The present study emphasizes that the water retention and increased plasma volume in such cases may result in serious and even fatal pulmonary edema. The remarkable feature of the water retention in the present cases was that no diuresis occurred in spite of elevation of the serum albumin to high normal or above normal levels, and in spite of significant increases of plasma volume. Rather, there was even a distinct tendency to oliguria. Since there was no lowering of blood pressure nor evidence of other factors which might reduce renal blood flow, the possibility of augmented antidiuretic activity must be considered. In this connection the observations of Ralli and her associates[13] are of particular interest, since they offer objective evidence of an increased concentration of antidiuretic substances in the urines of cases of cirrhosis with ascites.

**Summary and Conclusions.** 1. In 6 cases of hepatitis and, or, cirrhosis of the liver, the administration of salt poor human albumin in large amounts failed to provide decisive information as to its possible therapeutic value. In 2 of the cases dramatic improvement ensued, but in both there was reason to believe that other factors were of greater significance. In the remaining 4 there was neither subjective nor objective evidence of improvement.

2. Fever and water retention were commonly encountered. The latter repeatedly resulted in pulmonary edema, with a fatal outcome in one instance. It was remarkable that coincident with an elevation of the serum albumin to 5 gm. per 100 cc. or higher, the plasma volume and body weight increased, often with signs of pulmonary edema, yet there was no diuresis, in fact the urine volume tended to diminish. The possibility is considered that this lack of diuresis was due to antidiuretic activity such as reported in cases of cirrhosis by Ralli and associates.

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# PROZONE PHENOMENON IN THE SERODIAGNOSIS OF SYPHILIS

## A Clinical Study

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During the past several years considerable interest has been shown in the false positive reactions occurring in the serodiagnosis of syphilis. Less attention, however, has been given to the cases of untreated active syphilis in which serological tests were reported as negative. This has led to diagnostic confusion and failure to apply effective therapeutic procedures. Survey of the literature fails to reveal any significant clinical investigations relevant to this problem. The purpose of this report is to bring attention to this potentially important source of diagnostic error.

It is well known that serological tests may be negative in certain types of syphilis. These include early or congenital syphilis, treated cases, and certain forms of cardiovascular and cerebrospinal syphilis. In addition, there remain those whose sera are negative until diluted. These fall into the group manifesting the prozone (prezone or zone) phenomenon as illustrated by the 5 cases described in this paper.

Bacteriologists have long recognized the fact that varying reactivity could be noted in different antigen-antibody ratios. Early in the study of immunology it was observed that some sera which would agglutinate bacteria in high dilutions would fail to agglutinate when they were mixed with the bacteria in concentration.[13] Ehrlich, as cited by Zinsser and Bayne-Jones, designated this ratio where agglutination failed to occur as "the proagglutinoid zone." Eisenberg and Volk[4] were the first to study the phenomenon in detail, theorizing as to its cause on the basis of Ehrlich's conception of agglutinin structure. In 1926, Dean and Webb[10] investigated the character of the various zones occurring in precipitation reactions, designating the zone of maximal flocculation as the optimal proportion or ratio. Weiner,[11] in his studies in 1937 on the Kline test for syphilis, found sera which, though giving a weak reaction on the direct test, became more distinct on dilution. Subsequently, it was noted that a negative Kline exclusion or Kahn presumptive test does not exclude the possibility of a positive reaction by other technics.[5] Some syphilitic sera are detected only by a less sensitive procedure. Contradictory results are particularly common when both a flocculation and a complement fixation test are used, the former being peculiarly susceptible to zone reactions. Stowe[9] observed the occurrence of negative (prozone) Hinton

reactions in 4 patients, demonstrating that the more sensitive the flocculation test, the more susceptible it is to prozone reactions. Wiener[12] reported in 1940 on the United States Public Health Service investigation by 15 laboratories of the various serological tests for syphilis on 213 known syphilitic sera. Seven sera were found to be falsely negative by two or more laboratories. As the number of units of reagin increased, so did the uniformity of results except for prozone reactions occurring in the Hinton tests. Myers and Perry[8] pointed out that despite the fact that serologists were acquainted with the prozone phenomenon, many laboratories, using one or more of the more recently developed flocculation tests, could readily fail to detect a prozone reaction.

Kahn,[7] in his observations on the "optimal zone reaction" found that certain of the so-called seronegative syphilitic sera became positive when more antigen-antibody ratios were employed. The standard Kahn test employs serum: antigen ratios of 3:1, 6:1, and 12:1. When ratios ranging from 1:1 to 1:100 were employed, positive results were obtained in syphilitic sera which were negative according to the standard Kahn method. Kahn believed that each individual serum has an optimum zone of reactivity, and that negative readings are due to disproportionate amounts of antibody and antigen. A serological pattern common in late syphilis is a negative reaction for standard Kahn and high serum:antigen ratios of 24:1 to 100:1, but a positive reaction in low serum:antigen ratios of 1:1 and 1:2.

INCIDENCE. The occurrence of zone effects in the Kline and Hinton tests, according to Greene and Breazeale,[5] is only about 1 in 1000 and should therefore not prove a great source of error. Myers and Perry,[8] on the other hand, tested more than 2000 specimens with negative Kline-exclusion reactions and found zone reactions in 0.3%. If all routine examinations done during that time were included, the incidence became 0.15%. This increased to 1.7% with the inclusion of atypical "doubtful" tests which the authors believed would have been interpreted as negative by many serologists.

THEORETICAL CONSIDERATIONS. In flocculation tests 3 zones are found to exist —the zone of antigen excess (or antibody deficiency), the central equivalence zone, and the zone of antigen deficiency (or antibody excess). Reactivity in the first and third zones may be partially inhibited or fail to occur altogether. The optimal zone (that is, the central equivalence zone), may be demonstrated by varying either the antigen or antibody concentrations. In any one system the optimal ratio is not necessarily a fixed value. When the antigen content is fixed and the antibody concentration varies, the optimal ratio will frequently differ from the one obtained when the antibody concentration is constant and the antigen content is the variable. A difference is found also in precipitation and in agglutination reactions. In the former, precipitation is derived largely from the antibody; in the latter, floccules consist mainly of the antigen-carrying material. Several zone phenomena occur also in the complement fixation reactions.[2] Among these, there has been noted one type analogous to the flocculation prozone described above, namely, due to excess antigen or serum. In addition, there are a number of factors peculiar to the use of the sheep cell-amboceptor hemolytic system which contribute to false negativity in the complement-fixation reaction. Zone reactions based on antigen-antibody ratios are not noted in the spinal fluid. The conventional zone reaction occurring in the colloidal gold test on spinal fluid or its many modifications has been

shown to depend on the concentration and ratio of albumin to globulin. Here the albumin tends to prevent flocculation and the globulin to further it.

Clinical Forms of Syphilis. A correlation between the frequency of the prozone phenomenon and the various forms of syphilis has not been established, but it appears to occur predominantly in the late forms of active syphilis. The reports in the literature are concerned almost exclusively with the serological aspects of zone reactions. Heyman[6] reported 1 case with the diagnosis of latent syphilis and simple gastritis. Stowe[9] found 4 cases with prozone reactions (Hinton tests only, the Kahn and Kline tests being positive); 3 had cerebral syphilis and the fourth condyloma lata. In the 6 cases of Myers and Perry,[8] the clinical diagnosis was mentioned only in two. One patient had far-advanced general paresis and the other acute syphilitic periostitis of the leg and "cardiac symptoms." In the only report of the prozone phenomenon in early syphilis, Callaway[1] found negative or doubtful serologic tests in "many patients" with secondary syphilis; the quantitative tests showed titers as high as 512 Kahn units.

Fig. 1.—Case M. H.

The following cases illustrate the prozone phenomenon observed by the authors on the teaching service of a large municipal hospital.

**Case Abstracts.** Case 1. M. H., a 50 year old colored housewife, was admitted to Gallinger Municipal Hospital on August 23,

1945, with hoarseness and dyspnea of 4 weeks' duration, followed by a productive cough, weight loss, weakness, and fever. One year previous she noted a small, nodular, painless, and non-pruritic lesion on her right arm. It increased in size progressively, became reddened, scaly, and ulcerated. One month before admission, a similar area appeared on the right cheek, spreading over the nose and down the neck; later another nodule appeared on the forehead.

On admission she was moderately dyspneic, with a temperature of 102.4° F. A large, scaly, plaque-like lesion extended over the right antecubital space and arm for approximately 20 cm. (Fig. 1). Similar lesions were noted on the left malar region, nose and neck. Facial lesions were markedly hypertrophic with enlargement and distortion of the nose, resulting in a leonine appearance strongly suggestive of leprosy. Over the right supra-orbital ridge, a discrete nodule approximately 2 by 3 cm. was present. Later it increased in size and ulcerated, as shown in Fig. 2. Such nodules could be distinguished in the periphery of the face and arm lesions, coalescing to form large areas of destruction and marked scarring. No other significant findings were present except hoarseness and coarse rales at the base of the left lung posteriorly. Neurological examination revealed no sensory changes.

FIG. 2.—Case M. H.

*Laboratory examinations:* Hemogoblin ranged from 8.57 gm. to 10.5 gm. per 100 cc.; red blood cells from 3,900,000 to 4,500,000 per cu. mm. The leukocyte count on admission was 10,000 but later fell to 4,500 per cu. mm. with a normal differential at all times. Urinalysis was essentially nega-

tive. The corrected sedimentation rate was 0.35 mm. per min. (Rourke-Ernstene). The serum proteins were 7.22 gm. per 100 cc. of blood with the albumin 4.16 gm. and the globulin 3.06 gm. Twenty-four hour sputum specimens were negative for acid-fast bacilli on 15 occasions; gastric washings on 4 occasions. Two cultures from the lesions were negative for fungi and scrapings of the nasal mucosa were negative for *Mycobacterium leprae*. The tuberculin test (P.P.D.) was negative in two strengths.

*Serological studies* were as follows: The Kahn test was doubtfully positive on August 24, 1945, negative on August 29, positive on September 24, and negative on October 10. The quantitative Kahn on October 12 was 4 plus in a dilution of 1:2048. The spinal fluid protein was 38 mg. per 100 cc. and the colloid gold curve was 0002100000.

*Roentgenogram* of the chest on October 8 revealed mottling and fibrotic changes at the base of the left lung which were unchanged on December 4. Roentgenogram of the hands revealed no evidence of sarcoidosis. Direct laryngoscopic examination on September 18 revealed marked edema of the larynx making it difficult to visualize the vocal cords. On October 30, some improvement in the edema was noted but a bronchoscopic examination was deemed inadvisable at the time. Biopsy of the skin lesions on September 8 was interpreted as showing a chronic inflammatory process.

FIG. 3.—Case F. Y.

*Course:* The patient became asymptomatic

24 hours following admission except for hoarseness and the cutaneous lesions, the latter progressing despite local therapy. On November 5, bismuth subsalicylate was begun with immediate and dramatic improvement, healing of the skin lesions occurring centrally. Penicillin, 20,000 units intramuscularly every 2 hours, was given from November 14 to the date of her requested discharge on December 8, 1945. She received a total of 6 cc. of bismuth and approximately 6,000,000 units of penicillin. On discharge, the skin lesions had cleared completely. The hoarseness, which had remained unimproved for several weeks, disappeared just prior to her departure from the hospital. The patient failed to return for bronchoscopy, and the etiology of the pulmonary lesion, radiographically unchanged at the time of discharge, was not ascertained. The possibility of syphilitic involvement of the larynx or lungs could not be excluded with certainty. When seen at her home in April, 1947, the patient stated that she had been entirely asymptomatic since leaving the hospital. The sites of the cutaneous lesions were marked only by hyperpigmentation and minimal scarring. Further examination was refused except for a serologic re-check which was 4 plus in a dilution of 1:256. The diagnosis was cutaneous ulcerative gummata with prozone phenomenon.

Case 2. F. Y., a 71 year old colored male, was admitted to Gallinger Municipal Hospital on March 5, 1947, complaining of chronic ulcers on both legs for 2 years, undiagnosed as to cause and not benefited by attendance at several dermatologic clinics. Increasing dyspnea on exertion had been noted the past year. Approximately 50 years ago he had received local treatment for a penile ulcer.

On admission the systolic blood pressure was 155, the diastolic 65. He was in congestive heart failure with regular rhythm and cardiomegaly with a systolic and diastolic aortic murmur. On the moderately edematous lower extremities, undermining ulcers were present with a striking hyperkeratosis of the surrounding skin (Fig. 3). The ulcers were covered with a grayish-white, foul exudate. Routine laboratory procedures were noncontributory. Cultures from the lesions revealed no significant bacteria or fungi, and biopsy was interpreted as chronic granuloma. The qualitative Kahn test was negative.

The ulcers failed to improve despite vigorous local therapy and restoration of cardiac compensation. Because the diagnostic problem was similar to the first case, a quantitative Kahn test was obtained. It was positive in a titre of 1:2048. The complement fixation test at this time also was positive. Bismuth subsalicylate was administrated for 3 weeks followed by 10,000,000 units of penicillin. Healing occurred with residual atrophic scars following bismuth and penicillin therapy; he was discharged to the outpatient department. In view of the persistent high titre, (1:512) 5 months later he received an additional 6,000,000 units of penicillin. The quantitative titre then decreased to 1:256 and the originally negative qualitative Kahn was now a 2 plus positive. The diagnosis was gummatous ulcerations of the legs, syphilitic heart disease with aortitis and aortic insufficiency, and prozone phenomenon.

Case 3. M. S., a 63 year old colored female, was admitted to Gallinger Municipal Hospital on April 8, 1947, complaining of a draining breast abscess since August, 1946. Biopsy during a prior hospitalization elsewhere in February revealed chronic suppurative mastitis. Therapy, including irradiation, was ineffective and she left the hospital with the breast lesion unhealed and draining. She was bedridden at home until the development of a decubitis ulcer prompted rehospitalization.

She was afebrile on admission. Examination revealed a cronically ill, poorly nourished female with a large decubitus ulcer over the sacrum. An abscess occupied the upper, outer quadrant of the right breast. Multiple sinuses with a serosanguinous discharge were present. Centrally there was deep ulceration with a malodorous, purulent material covering the base. There was no induration of the breast tissue and no regional lymph node enlargement.

The hemogoblin was 12.8 gm. per 100 cc., the erythrocyte count was 2,840,000 per cu. mm., and the leukocyte count was 9200 per cu. mm. with 90% neutrophils. The corrected sedimentation rate was 46 mm. per hour (Wintrobe method). Culture from the breast lesions revealed *Staphylococcus aureus*, streptococci, proteus, and *E. coli*. No fungi could be cultured. Studies for acid-fast organisms including gastric washings were negative. Numerous determinations of serum proteins ranged from 5.04 gm. to 8.60 gm. per 100 cc., but unfortunately the levels were too fluctuant and erratic to be correlated with the clinical course. The albumin-globulin ratio was not disturbed. The initial Kahn and Mazzini tests were reported as doubtful. Subsequent Kahn and Mazzini tests were positive, the former being 2 plus. A quantitative Kahn test was then obtained and was 4 plus in a 1:128 dilution. Skeletal and chest roentgenogram were non-contributory. A biopsy of the breast revealed a subacute inflammatory reaction.

On a high calory and protein diet, intensive parenteral protein therapy, and local care of

the breast lesion and decubitus ulcer, there was no response except for a slight diminution in the amount of discharge from the breast lesion. In view of the positive serologic tests and the patient's failure to respond to therapy she was started May 3 on bismuth subsalicylate, 0.12 gm., twice weekly. Immediate and marked improvement was noted in the breast lesion followed later by granulation of the decubitus ulcer. The patient was discharged June 21, 1947, with both lesions completely healed.

This case illustrates the prozone phenomenon in a patient with a chronic ulcerative breast lesion that healed during the bismuth therapy .

Case 4. P. B., a 43 year old colored male, was referred to Gallinger Municipal Hospital in April, 1948, by the George Washington University Medical Clinic with a diagnosis of aneurysm of the right subclavian artery. Syphilis was denied and several blood tests during the past few years had been negative. The systolic blood pressure was 130, the diastolic 70 in both arms. The heart was moderately enlarged. A blowing diastolic murmur was heard at the left sternal border. The qualitative Kahn test was negative, but a quantitative test was 4 plus in a titre of 1:16. Attempted cellophane wrapping confirmed the presence of an aneurysm. This patient with syphilitic heart disease and aneurysm of the subclavian artery also demonstrates the prozone phenomenon.

Case 5. H. M., a 66 year old white male, was seen in another hospital in June, 1948, in acute left ventricular failure. Examination revealed marked cardiac enlargement, increased supra-cardiac dullness, aortic insufficiency and a protodiastolic gallop rhythm. Roentgenogram of the chest revealed a saccular aneurysm of the ascending aorta, cor bovinum, and pulmonary engorgement. The qualitative Kahn test was negative; the quantitative Kahn test was 4 plus in a dilution of 1:256. The Wassermann test was a 4 plus positive. The patient died suddenly 4 days following admission. Necropsy revealed a syphilitic aortitis; the aneurysm of the ascending aorta had ruptured into the pulmonary artery through the sinus of Valsalva of the posterior aortic cusp. This patient had cardiovascular syphilis with the prozone phenomenon.

**Comment**. The cases reported here (Table 1) demonstrate the prozone phenomenon as shown by negative or equivocal serological tests which became strongly positive upon dilution of the serum.

In the first case (M. H.), diagnosis was delayed over 7 weeks because of failure to consider the possibility of a prozone phenomenon. Prolonged hospitalization and many expensive diagnostic tests resulted needlessly. The patient was seen by numerous competent internists, dermatologists, syphilologists, and other consultants. The diagnosis of syphilis was not considered due to the marked activity of the lesions and the negative serologic tests. The clinical characteristics of the lesions and their prompt healing under antisyphilitic therapy (bismuth) confirmed the serological diagnosis of syphilis which was made eventually.

The appearance of the breast lesion in the third case (M. S.) had been altered by Roentgen-ray therapy, and the clinical features were characteristic of no specific lesion. Vigorous therapy directed at elevation of the depressed

TABLE 1.—CLINICAL DATA OF CASES SHOWING THE PROZONE PHENOMENON

| Patient | Lesions | Serology | | Result of Treatment | |
|---|---|---|---|---|---|
| | | Qualitative | Quantitative | Clinical | Serological |
| M.H. | Ulcers of face and arm | Doubtful<br>Negative<br>Positive<br>Negative | 1:2048 | Cure | 1:256 |
| F.Y. | Ulcers of legs and Cardiovascular syphilis | Negative | 1:2048 | Cure of ulcers | 1:256 |
| M.S. | Ulcer of breast | Doubtful | 1:128 | Cure | — |
| P.B. | Cardiovascular syphilis | Negative | 1:16 | Died | — |
| H.M. | Cardiovascular syphilis | Negative | 1:256 | Died | — |

serum proteins may have contributed significantly or solely to the recovery. The erratic reports of the serum proteins, however, make this a difficult factor to evaluate. On the other hand, the definite prozone phenomenon in the Kahn test and the failure to respond to therapy until bismuth was added suggests a syphilitic basis for the breast lesion.

The second, fourth, and fifth cases clearly demonstrate that the prozone phenomenon represents one cause for the negative serologic tests frequently reported in cardiovascular syphilis.

The variability of different serums should keep the clinician constantly alert and suspicious of the serology reported as negative. The routine use of 2 serological tests of different sensitivity or the use of flocculation and complement-fixation tests is highly desirable. Clinical suspicion of a possible syphilitic process should always prompt quantitative studies when routine serological studies are negative or equivocal. The routine use of the quantitative test, although desirable, is not practical in most laboratories due to the additional work involved.

**Summary and Conclusions.** Five cases of late syphilis with the prozone phenomenon are reported. On the basis of these cases and the investigation of others in this field, it is concluded that due to the prozone phenomenon, negative or doubtfully positive serologic tests do not exclude the presence of late active syphilis.

The prozone phenomenon is not restricted to any particular form or stage of syphilis, occurring in active and latent syphilis, in congenital or acquired forms, in central nervous system, skin, and other types of involvement, but has never been reported in primary syphilis. It is a not uncommon cause of negative serologic tests in cardiovascular syphilis.

Two diagnostic tests of varying sensitivity should be employed routinely in the serodiagnosis of syphilis. If impracticable or if clinical manifestations suggest the possibility of a syphilitic condition despite negative or equivocal tests, quantitative serological tests should be done.

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# RECOVERY FROM UREMIA

## A REPORT OF FIVE CASES

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There has been a renewed interest in the phenomenon of acute azotemia not due to acute or chronic nephritis[3,24] and several mechanisms have been advanced to explain the diminished urinary output. It has been suggested that the damage to renal vasculature and parenchyma in anuria following burns,[4] shock,[7] premature placental separation,[20] and crushing trauma[6,23] is due to a circulating toxin and there is experimental evidence that such a toxin may exist in macerated muscle.[2,19] Some cases of sulfonamide poisoning may fall into this group.[18,28] Another mechanism offered to account for anuria or oliguria associated with shock-like states is a diminished renal blood flow and consequent tissue anoxia which depends upon the general fall in arterial blood pressure.[7,9,13,17,21,22,25] That anuria in shock might be the result of a mechanism unrelated to the alteration in circulatory dynamics is indicated by the demonstration of the presence of a humoral antidiuretic substance in subjects in the post-syncopal state.[5] A third mechanism is suggested by the experiments of Trueta and others[27] demonstrating reflex nervous constriction of renal cortical circulatory pathways. Stimulation of the proximal ends of severed peripheral nerves resulted in a diversion of the renal blood flow "wholly or partly from the cortex and short-circuited it through medullary (especially subcortical) blood channels" thereby rendering the cortex ischemic. There has been considerable discussion as to which of these mechanisms is responsible for the acute azotemias occurring under the different circumstances mentioned. The great diversity of anatomical changes, all the way from severe cortical necrosis[11,12] and lower nephron nephrosis[23] to minimal changes in the proximal tubules[1] suggest that one or more of these mechanisms may operate at different times and that no one can adequately explain the findings in all cases. Recently, Bell and Knutson[1] reported 84 cases of azotemia occurring terminally in a variety of conditions in which the kidneys were anatomically normal in all but 20 cases, and these showed only mild to severe hydropic degeneration of the proximal convoluted tubules.

In view of the apparent rarity of recovery from severe degrees of acute azotemia, it seemed important to report 5 cases which, because they survived and subsequently showed adequate renal function, probably represented cases similar to those of Bell and Knutson[1] rather than those with more severe degrees of structural

change. That these 5 cases recovered on vigorous therapy with fluids intravenously and by mouth suggests that dehydration may have affected renal hemodynamics sufficiently to result in acute nitrogen retention.

**Case Reports.** *Case 1.* A 55 year old woman was transferred to Goldwater Memorial Hospital on November 17, 1946, from an institution for indigent homeless because of diarrhea of 3 days' duration. She had been treated with both sulfasuccidine and sulfadiazine without improvement and was sent to the hospital when listlessness and oliguria developed. Her past history was irrelevant except for hypertension and a sudden left hemiplegia at the age of 47.

Physical examination revealed an obese woman who was weak and lethargic and incontinent of urine and feces but who responded when roused. Her skin was dry and her tongue coated. The heart was slightly enlarged to the left and there was a soft apical systolic murmur. Blood pressure was 132/90 mm. of mercury. The abdominal wall was lax and redundant and was slightly edematous. There was minimal edema of ankle and thigh. There was evidence of a residual left hemiplegia with hyper-reflexia. Babinski and Hoffman signs were present on that side.

On admission, urine examination showed a specific gravity of 1.010 and 1+ albumin. The centrifuged sediment contained a few erythrocytes, 10 to 20 leukocytes and many granular casts per high power field. Sulfonamide crystals were not seen. Culture showed B. proteus. Red blood cell count was 4,100,000, leukocytes 10,700 per c.mm.; hemoglobin 13.0 gm. The blood urea nitrogen was 126.4 mg. per 100 cc. and the sulfadiazine level 4.5 mg. Stools were guaiac-positive but negative on culture for pathogens. The chest was clear on Roentgen-ray photography. Electrocardiograms showed prolongation of the Q-T interval, depression of the S-T segment in Leads I, II, and $CF_4$ and depression of the T wave in leads I and $CF_4$.

The impression was that of azotemia due to dehydration and therapy with intravenous fluids was initiated. The blood urea nitrogen rose on the following day to 137.5 mg. per 100 cc. but then fell progressively to normal over a period of 9 days. The diarrhea subsided spontaneously during the next several days after admission. The patient became alert. In an electrocardiogram taken after recovery, the Q-T interval had decreased and the other abnormalities had disappeared. Maximum urine specific gravity rose to 1.015 and the urea clearance was established at 68% of normal. The urine cleared gradually and at discharge showed only a trace of albumin and occasional leukocytes.

*Case 2.* A 78 year old Irish male was hospitalized at Goldwater Memorial Hospital on December 10, 1946, because of diarrhea of 6 days' duration which failed to respond to paregoric or sulfadiazine. He grew progressively weaker and became severely dehydrated. Digitalis was given when the blood pressure fell from 170/90 to 115/80 mm. of mercury.

On physical examination, he was disoriented and semicomatose. The skin was dry, the eyeballs soft and the tongue, palate and pharynx coated with a brown deposit. Breath sounds were distant and the chest hyperresonant. The rhythm of the heart was irregular and shown by electrocardiogram to be due to a wandering pacemaker. Blood pressure was 110/60 mm. of mercury. The abdomen was doughy. The radial arteries were markedly sclerotic. The hands and feet were cool and showed a purplish mottling.

On admission, the urine revealed 1+ albumin and on microscopic examination, rare erythrocytes, 3 to 5 leukocytes and occasional casts per high power field. Sulfadiazine crystals were not seen. There was hemoconcentration. Stool cultures were negative for pathogens. Blood urea nitrogen was 154.4 mg. per 100 cc.

The patient was considered to be suffering from azotemia secondary to dehydration and the administration of intravenous fluids consisting of 5% glucose in physiological saline and distilled water was begun. On this regimen, drowsiness lessened and by the 4th day, adequate fluid intake was managed orally. The

diarrhea responded slowly to sulfasuccidine and intravenous fluids but the blood urea nitrogen fell promptly to 18.5 mg. on the 10th hospital day. Digitalis was discontinued and was not further required. Standard urea clearance, shortly after clinical recovery, was 25% of normal and 4 months later rose to 43% of normal. Blood urea nitrogen was 24.5 mg. and urine specific gravity 1.018 at this time.

*Case 3.* The patient, a 74 year old colored female was transferred from another hospital to Goldwater Memorial Hospital on July 7, 1944, because of gangrene of the right big toe. She was a known hypertensive of about 4 years' duration and was fairly well until about 4 months prior to admission when she developed a sore on the right big toe which, in spite of various attempts at therapy, became gangrenous.

Physical examination revealed an elderly colored female in no apparent distress. Arcus senilis was present. The heart was enlarged to the left. There was a systolic murmur at the apex. The abdomen was normal. The right big toe was malodorous and necrotic. The dorsalis pedis and popliteal pulsations were bilaterally absent.

On admission, the urine examination showed a trace of albumin and the specific gravity was 1.014. The blood urea nitrogen was 15.1 mg. Blood Wassermann was negative. The electrocardiogram showed a left deviation of the electrical axis. Roentgen-ray revealed that the heart was enlarged to the left. The aorta was dilated and calcified. Roentgen-ray of the lower extremities showed calcification of vessels and decalcification of bones.

In July, 1944, the patient's right big toe was amputated. The course following the operation was uneventful until a bout of broncho-pneumonia occurred in December, 1945. In January, 1947, the patient was transferred to the medical service because of slowly developing dyspnea, orthopnea, intermittent substernal discomfort, and edema despite the use of digitalis and ammonium chloride. Because edema of lower extremities was marked and congestion of lungs by Roentgen-ray was intense, mercupurin therapy was started. Following rather liberal administration of this diuretic, the patient became disoriented and drowsy on Feburary 10, 1947. The tongue and skin were dry. Involuntary twitchings of the muscles of extremities were observed. Blood urea nitrogen was found to be 89.2 mg. per 100 cc., carbon dioxide combining power 30 volumes % and calcium 10.4 mg. per 100 cc. Parenteral fluids were administered by clysis but apparently in insufficient quantity because she became even less responsive, reacting only to painful stimuli. Her abdomen became markedly distended. Three days later (February 13, 1947), blood urea nitrogen was 114 mg. and the carbon dioxide combining power 23 volumes %. Intravenous fluids were then given copiously and the patient began to improve. The blood urea nitrogen fell rapidly to normal values, the carbon dioxide combining power returned to normal and the patient improved greatly. Renal function studies after recovery showed phenolsulfonphthalein excretion of 40% at the end of 2 hours and urea clearance of 53% of normal. Subsequent urinalyses showed specific gravities of 1.010 to 1.012 with a trace of albumin. The patient's renal status has remained unchanged since.

*Case 4.* The patient, a 70 year old Puerto Rican man was transferred from another hospital to Goldwater Memorial Hospital with a diagnosis of hypertensive and arteriosclerotic heart disease and possible cirrhosis of the liver. Patient's history was very difficult to obtain because of his stupor and language difficulty. He was apparently well until about 4 months prior to hospitalization when he began to complain of epigastric pain and occasional bouts of vomiting and noticed loss of weight. Subsequently, he experienced bouts of precordial pain and edema of the ankles. There was no history of dyspnea or orthopnea. Progressively failing vision beginning 4 years prior to admission lead to enucleation of the left eye. Otherwise, his past history was uneventful. At the hospital from which he was transferred, the level of creatinine in the blood was said to be 3.5 mg. per 100 cc. and the blood urea nitrogen 105 mg. His blood Kahn was negative.

On admission, the patient appeared acutely ill and semi-stuporous. He showed evidence of weight loss and considerable dehydration. There was no dyspnea or orthopnea. His left eye was enucleated and the right eye showed a corneal opacity. His tongue was dry and coated. His lungs were clear to percussion and auscultation. The heart was enlarged to the left. There was a faint systolic murmur at base and apex. Blood pressure was 150/70 mm. of mercury. There were no abdominal masses palpable. The extremities were not edematous and arterial pulsations were good.

On admission, hemoglobin was found to be 14.0 gm. red blood cell count 7,000,000, white blood cell count 10,800 per c.mm., and hematocrit 56%. The urine showed a specific gravity of 1.009, a trace of albumin and 20 to 30 leukocytes per high power field. The blood urea nitrogen was 98.8 mg. per 100 cc. The total serum protein was 7.8, albumin 4.1 gm. per 100 cc. On the following day, after institution of intravenous fluids, the red blood cell count had fallen to 4,200,000 per c.mm., the hematocrit to 43%. However, the blood urea nitrogen remained elevated (112.3 mg. with a carbon dioxide combining power of 49 volumes %). Total protein was 5.6 gm. per 100 cc. after institution of therapy. The cholesterol was 191 mg. The calcium was 9.2 mg. and the alkaline phosphatase was 11.9 King-Armstrong units. Roentgen-ray photograph of the chest showed a slight accumulation of fluid at the right base. The remainder of the pulmonary field was clear. The heart was enlarged and the aorta somewhat widened and tortuous. The electrocardiogram was essentially normal. The admission impression was hypertensive and arteriosclerotic heart disease. The renal lesion was thought to be chronic glomerulonephritis or chronic pyelonephritis with uremia.

The patient was treated rather vigorously with infusions of glucose in saline and glucose in water and intramuscular penicillin. Although the prognosis was very grave because of semi-coma, Cheyne-Stokes breathing and the high level of urea nitrogen in the blood, the patient began, gradually but definitely, to improve. Lethargy gave way to alertness and the patient became oriented. The blood urea nitrogen level fell from 112 mg. to normal. The improvement took place during a period of 2 weeks.

Following recovery, investigation showed that the patient had relatively good renal function. The phenolsulfonphthalein excretion was 57% at the end of 2 hours. The urea clearance was 83% of normal. Fishberg concentration test yielded a specific gravity of 1.020. The urine gradually cleared. Further renal studies showed a filtration rate of 76 cc. per minute (normal, 100 to 125 cc. per minute), para-amino hippuric acid clearance of 320 cc. per minute (normal 400 to 600 cc. per minute). The urine flow was 3 to 4 cc. per minute. Retrograde pyelogram was essentially normal. He was discharged to be followed in the out-patient clinic. It was believed that the patient's principal difficulty was dehydration which resulted in prerenal azotemia. The cause of the dehydration was not ascertained.

*Case 5.* The patient, a 56 year old widow, was admitted to Lenox Hill Hospital on April 23, 1947, for possible intestinal obstruction. Her chief complaints were nausea, vomiting, mild dyspnea, and obstipation of 11 days' duration. This was preceded by epigastric pain which persisted for 2 days. She had no bowel movements, but did continue to pass flatus. Vomiting 3 or 4 times a day persisted. The vomitus was bile stained but never fecal in character. In the week prior to admission, she had moderate degree of lower abdominal pain aggravated by motion and became extremely weak.

Ten years ago, she had been told that she had heart disease. One year ago, she began to have ankle edema and exertional dyspnea that became rather marked on climbing one flight of stairs. She was put on digitalis leaf, 0.1 gm. a day, which she continued to take until 2 months prior to admission, when she discontinued the drug.

On physical examination, she was extremely lethargic and acutely ill. Hyperpnea was marked and a uremic odor

was noted on her breath. Her pupils were equal, round, widely dilated and did not react to light. Eye grounds were essentially normal. The tongue was beefy and dry. A few scattered rales were heard at both lung bases posteriorly. Blood pressure was 100/80 mm. of mercury. Heart sounds were distant and of poor quality. A soft blowing systolic murmur was heard over the entire precordium. Roentgen-ray examination of the heart revealed some enlargement of the left ventricle and calcification and dilation of the arch of the aorta. The electrocardiogram was essentially normal with the exception of slight slurring of the QRS complex and a prolongation of the P-R interval (0.22 sec.). The abdomen was but slightly distended and the liver edge was palpable 1 cm. below the costal margin. There was slight edema of the legs and arms. Reflexes were present but sluggish.

The blood urea nitrogen was found to be 110 mg. per 100 cc. and the carbon dioxide combining power was 22.3 volumes %. Hemoglobin was 12 gm.; red cell count was 4.3 million per c.mm.; leukocytes numbered 16,300 per c.mm. with 87% granulocytes. Plasma chlorides were 584 mg. per 100 cc. (expressed as sodium chloride). Urine was pale yellow with a specific gravity of 1.002. Microscopic examination of the urine revealed only occasional hyaline and granular casts and about 10 white blood cells per high power field.

Thus the patient, who appeared to have an intestinal obstruction, was quite obviously in a state of uremia. The presence of an obstructive lesion also remained a possibility, but in the absence of marked distention and with the persisting passage of flatus, this was thought to be, at most, an incomplete one. Hence the uremia was considered the main problem and she was accordingly given fluids to the extent of 1500 to 2000 cc. daily in the form of glucose in distilled water, at first intravenously, and thereafter by clysis. After an initial saline infusion, further sodium was withheld because of her cardiac status. During periods when she was reactive, she remained mentally confused and disoriented. She showed considerable muscular irritability but had no convulsions. Urine output was quite small for the first 3 days, totalling about 500 cc. Thereafter, it increased and averaged about 800 cc. daily. The urine was poorly concentrated (specific gravity below 1.005) and was negative for albumin. At no time did microscopic examination of the sediment show more than occasional casts, white blood cells and red blood cells.

An episode of acute pulmonary edema occurred on the 5th day of hospitalization for which she was digitalized. Several days later, slow auricular fibrillation (ventricular rate of 90 per minute) was found to be present. The rhythm failed to revert to normal sinus with quinidine. For nearly 2 weeks, she remained in a semi-stuporous state and had no bowel movements. She was, however, taking nothing by mouth and, since she continued to pass flatus and distention did not develop, she was not thought to be obstructed. Blood urea nitrogen had risen by the 11th hospital day to 153 mg. per 100 cc. Muscular twitching became marked and a loud pericardial friction rub developed. Then, during the next few days, she began to improve symptomatically, became more alert and oriented and took small amounts of fluid by mouth. The muscular irritability and pericardial friction rub disappeared. By the 14th hospital day, blood urea nitrogen had dropped to 80 mg. and the carbon dioxide combining power had risen to 32 volumes %. Following this, she progressed rapidly and 2 weeks later, the blood urea nitrogen was 12.5 mg. The clinical picture had shown an equally dramatic improvement.

Urea clearance done at this time was 42% of normal and the maximum urine concentration obtained was a specific gravity of 1.014. It was evident that some impairment of kidney function was present but even assuming that her kidney function was the same before this episode (it may well have been better), it was not in itself sufficiently impaired to have accounted for the development of uremia.

The course was thereafter uneventful. With ingestion of food and fluids, there followed normal bowel function and

TABLE 1. URINE AND BLOOD ANALYSIS VALUES DURING ILLNESS AND AFTER RECOVERY IN 5 CASES OF UREMIA

| | *DURING ILLNESS* | | | | | *AFTER RECOVERY* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *URINE* | | | *BLOOD* | | *URINE* | | *RENAL FUNCTION TESTS* | | | *BLOOD* | |
| *Cases* | *Max. Sp. Grav.* | *Sediment* | *Alb.* | *Max. Urea Nitrogen Mg./100 cc.* | *$CO_2$ Comb. Power Vol. %* | *Max. Sp. Grav.* | *Sediment* | *Alb.* | *PSP Per Cent in 2 hrs.* | *Urea Clearance Per cent of normal* | *Urea Nitrogen Mg./100 cc.* | *$CO_2$ Combining Power Vol. %* |
| 1 | 1.010 | Few RBC. 10–20 WBC. Many granular casts. | + | 137.5 | | 1.015 | Normal | Tr. | | 68 | 14.0 | 78.0 |
| 2 | 1.015 | 3–5 WBC. Occasional casts | + | 154.4 | | 1.018 | Normal | 0 | | 43 | 18.5 | |
| 3 | | | | 114.0 | 23.0 | 1.012 | Normal | Tr. | 40 | 53 | 9.9 | 61.0 |
| 4 | 1.009 | 20–30 WBC. | Tr. | 112.3 | 43.0 | 1.020 | Normal | 0 | 57 | 83 | 8.9 | 53.0 |
| 5 | 1.002 | 10 WBC. Occasional hyaline and granular casts. | 0 | 153.0 | 22.3 | 1.014 | Normal | 0 | | 42 | 12.5 | |

Roentgen-rays of the gastrointestinal tract revealed no abnormality.

**Comment.** It is well known that so called extrarenal azotemia may be the result of many different conditions such as dehydration (low fluid intake, vomiting, and diarrhea), hemorrhage into the gastrointestinal tract, shock, diabetic acidosis, and subarachnoid hemorrhage. In those cases due primarily to dehydration it has been noted [1,14] that the urine specific gravity is often lower than one might expect, were it the result of dehydration alone. This would suggest some impairment of tubular function and indeed cast doubt on the concept that the retention of nitrogen was entirely extrarenal in origin.

An analysis of the cases which are the subject of this report shows the following common features (Table 1). All had blood urea nitrogens over 100 mg. per 100 cc.; Van Slyke determinations, when done, showed low carbon dioxide combining power; and urine specific gravity at the height of the azotemia was lower than on recovery, corroborating previous observations by others. The slight degree of albuminuria and the unimpressive number of formed elements on microscopic examination of the urine are evidence against the occurrence of an acute nephritis. The speed of recovery of renal function is also contrary to the behavior of either acute or chronic nephritis. There are however other conditions exhibiting acute renal insufficiency which deserve comment because of the clinical similarity to the present series of cases; that is, the syndrome of bilateral cortical necrosis[11,12] and anuria following sulfonamide administration,[18,28] not due to tubular obstruction by sulfa crystals. Although recovery was shown to occur in at least one case of cortical necrosis confirmed by biopsy,[8] the marked structural alterations in fatal cases, in contrast to the minimal changes in the cases of extrarenal azotemia described by Bell and Knutson,[1] makes the diagnosis of cortical necrosis in our group of patients seem unlikely. Sulfonamides were used in 2 of our cases, but recovery occurred despite continued use of the drug.

Isolated cases of recovery have from time to time been reported,[10,15,16,26] but in general a fatal outcome has been, more or less, expected when the blood urea nitrogen has exceeded 100 mg. per 100 cc. in cases of renal failure. Each of these cases occasioned the authors some degree of surprise by recovery, and, naive though that surprise may be, it was thought that there may be others who have despaired of helping similar patients although the possibility of recovery still remained. It is especially interesting that a friction rub, generally regarded as a terminal sign, developed in 1 case (Case 5). Recovery of 5 apparently hopeless cases is reported to emphasize the importance of a period of energetic treatment with intravenous fluids when there is the slightest evidence of dehydration or when the state of renal function prior to the episode of uremia is unknown.

**Summary and Conclusions.** Five cases of marked extrarenal azotemia with recovery are reported. The initial assumption in these cases was that they were in the terminal stages of chronic nephritis and that death was to be expected. The energetic use of intravenous fluids appeared to be the most important therapeutic procedure in their recovery.

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# ON THE OCCURRENCE OF HERPES ZOSTER IN CARCINOMA OF THE BREAST

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It is common knowledge amongst oncologists and radiotherapists that the incidence of herpes zoster in Hodgkin's disease,[15] leukemia and metastatic carcinoma is greater than in the population at large, although statistics on the subject are not available. On the basis of large surveys, herpes occurs in the proportion of 1 to 2% of all diseases of the skin,[8] while in the period of 1925 to 1935 it was observed in 0.06% of 200,000 admissions to Bellevue Hospital in New York.[9] With the exception of the studies by Pancoast and Pendergrass[15], and Craver and Haagenson,[5] most previous papers have been concerned with single case reports of herpes zoster in carcinoma and allied diseases. The observance of 16 cases of this disease entity in a survey of 406 cases of carcinoma of the breast, giving an incidence of 4%, prompts this clinical presentation.

Herpes zoster is generally conveniently classified into 2 groups: The idiopathic or primary, and the symptomatic or secondary, forms. The idiopathic herpes occurs in otherwise normal individuals, and characteristically produces a vesicular eruption which follows a zonal or segmental distribution and is accompanied by fever, leukocytosis and marked pain. At times the eruption may be delayed in onset, and the pain may simulate that of a "surgical abdomen". The local skin lesion is self-limited. However, post-herpetic pain may become a very distressing aftermath which may lead the patient to the radiotherapist if the early lesion has not had the benefit of irradiation.

In 1864, Mitchell, Morehouse and Keen[13] showed that irritation and not section of a nerve was the cause of zoster and similar eruptions. Later, in 1872, Mitchell[12] indicated that at some time in the history of a nerve injury it is common to see certain forms of eruption, which are herpetic, vesicular, or in the shape of bullae.

Head and Campbell[10] in 1900 in an elaborate paper gave a large number of facts regarding the origin and distribution of zoster. They found destructive changes in the posterior ganglia of the spinal cord and in the Gasserian ganglion, and degeneration in the nerves leading to the skin. They concluded that some agent chooses the posterior root ganglion for its selected activity, producing profound inflammatory changes, which in time give rise to the irritation of its nerve elements. In 1902, Van Harlingen[17] reviewed the reports as to the origin and nature of herpes zoster.

The present day conception of the disease regards a filtrable virus as the causative agent. Many workers in the field believe there is a close relationship between the virus of varicella and that of herpes zoster.[1] However, this claim lacks unanimity.[6]

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Secondary or symptomatic herpes has an obscure and mixed etiologic background, having been observed during and following a variety of disease entities. It is seen during the course of many infectious diseases such as pneumonia, influenza, meningitis, and tuberculosis. In addition, it has followed trauma, pressure from a spinal cord tumor,[11] intoxication by poisons, and various neoplastic diseases. Carrière[4] in 1895 reported a case of femoro-cutaneous zoster following cancer of the uterus. Although there was no cancerous infiltration of the nerve, there was parenchymatous neuritis and he thought that the neuritis was due to a local and direct action of cancer toxins. The obscure pathogenesis has prompted numerous reports of unusual inciting agents. Considering the reputed frequency of herpes zoster in cases of cancer, Craver and Haagenson[5] stated that, "it is peculiar that there are not more of these cases on record".

Idiopathic herpes zoster was subjected to careful histologic study on 3 autopsied cases by Denny-Brown and Adams.[7] These workers found degeneration of related motor and sensory roots, severe neuritis, unilateral segmental poliomyelitis, and localized leptomeningitis. They concluded that the phenomena of herpes zoster required more than the ganglionic lesion for their explanation, but depend in part on a poliomyelitis and motor neuritis.

Symptomatic zoster is seen in fairly frequent association with Hodgkin's disease. Pancoast and Pendergrass[15] in 1924 reported 4 cases of herpetiform eruptions in Hodgkin's disease and 1 case in ovarian sarcoma. They thought that herpes zoster occurred much more frequently in malignant conditions than generally was believed. Craver and Haagenson[5] encountered 7 cases of herpes zoster (2.1%), in 329 cases of lymphosarcoma, Hodgkin's disease, and leukemia. To them the clinical data suggested that the herpes zoster was due to involvement of the nervous structures by the tumor process. Barton and O'Leary,[3] who were able to demonstrate a leukemic infiltrate in the zosteriform lesion in a case of generalized herpes zoster, regarded the herpetic lesion as merely the "traumatic stimulus" which caused an influx of leukemic infiltrate into the affected site. Sometimes the zosteriform infiltrate is noted as late as 6 months after the appearance of herpes zoster.[2]

The existence of a symptomatic type of herpes zoster brought on by tumor metastases is denied by some investigators. Mumme[14] autopsied a case in which herpes zoster developed in the territory of the 11th and 12th thoracic and 1st and 2nd lumbar ganglia in a patient afflicted with metastatic seminoma of the 12th thoracic vertebra. The 12th thoracic spinal ganglion was shown histologically to be entirely destroyed by tumor masses which contained within them inflammatory infiltrates. The 11th thoracic and 1st and 2nd lumbar spinal ganglia were completely free of metastatic seminoma, but exhibited a non-suppurative spotty inflammation with plasma cells indicating a true ganglionitis. Mumme denies a symptomatic zoster because there was no chronological relationship between the destruction of the 12th spinal ganglion and the appearance of the herpes zoster, although the conclusion about the time relationship is not very clear from the case history. In addition, the zoster did not limit itself to the territory supplied by the 12th thoracic ganglion, but extended also to include the 3 adjacent vertebrae. The inflammatory changes which in greater or lesser degree were present in all 4 spinal ganglia presented exactly the same histological picture as those

TABLE I.--DATA ON 16 CASES OF HERPES ZOSTER AND CARCINOMA OF THE BREAST

| Case No. | Age | Date of Mastectomy | Post-op. Roentgen Therapy | Date of Appearance of Zoster | Side Involved and Segments | Site of Metastases | Date of Appearance of Metastases | Date of Death |
|---|---|---|---|---|---|---|---|---|
| 1 | 37 | 4/29/37 | x | ? | homolateral; segments? | T6<br>L2 | 5/6/40<br>1/13/42 | 8/7/43 |
| 2 | 42 | 9/10/36 | x | 9/15/37 | homolateral; L1 distribution | T9, 12, and L2 | 3/16/37 | Sept. 1939 |
| 3 | 49 | 4/28/37 | x | July 1937 | ? | cervical, supraclavicular, liver, lungs, pelvis, legs | 9/18/38 | unknown |
| 4 | 35 | 12/22/34 | 0 | ? | homolateral; segments? | C2, T9, 11, 12<br>ilium | 11/2/35 | 10/22/36 |
| 5 | 71 | none | 0 | 7/11/38 | homolateral; T4 and 5 | T5 | 8/3/38 | June 1939 |
| 6 | 60 | 6/16/39 | 0 | 1/22/43 | homolateral; segments? | bilateral pleural metastases | 1/22/43 | 7/27/43 |
| 7 | 43 | 1/3/33 | x | ? | homolateral; T7 and 9 | skin, liver, axilla | 9/22/33 | 12/14/33 |
| 8 | 45 | 4/19/35 | x | 10/28/36 | contralateral; segments? | lungs | 1/8/37 | April 1937 |
| 9 | 57 | 11/15/32 | x | May 1934 | homolateral; segments? | brain | at death | April 1935 |
| 10 | 45 | May 1933 | x | 4/28/36 | ? | lung, opposite breast | 10/30/36 | unknown |
| 11 | 75 | May 1932 | 0 | | homolateral; segments? | int. mammary nodes | 1/3/34 | 3/22/35 |
| 12 | 75 | 10/1/36 | 0 | 3/24/37 | homolateral; segments? | ? | at death | 9/21/38 |
| 13 | 74 | 5/15/35 | x | 9/26/38 | contralateral; facial | none | —— | alive on 12/6/44 |
| 14 | 64 | 11/15/32 | x | 6/8/34 | hemolateral; segments? | none | —— | 11/17/41; cerebral hemorrhage |
| 15 | 49 | 8/12/32 | x | 5/20/33 | hemolateral; segments? | none | —— | alive on 4/26/45 |
| 16 | 74 | 8/1/37 | x | 3/7/38 | contralateral; segments? | none | | alive on 4/1/45 |

customarily found in zoster of virus etiology. The seminoma metastases, in Mumme's opinion, merely acted as a predisposing factor to the invasion of the virus and the appearance of the disease.

Wohlwill[18] expressed a similar opinion concerning etiology as a result of his histological study. He found the involvement of the spinal ganglia was not constant either in the idiopathic or secondary type. While the dorsal ganglion was most frequently the site of involvement, the findings suggested that it could be produced by involvement of any point in the afferent portion of the reflex arc.

*Clinical Material.* The records of 406 cases of carcinoma of the breast seen by us at this hospital from 1932 to 1939 were investigated to complete previous studies at this institution on this subject.[16] Sixteen cases of herpes zoster were encountered, in 12 of whom there was evidence of metastatic disease either before or after the appearance of the cutaneous disease. The remaining 4 cases survived between 6 and 12 years after the herpetic attack with no evidence of metastatic malignancy.

**Case Abstracts.** CASE 1. S.S., a 37 year old white female, had a left radical mastectomy performed April 29, 1937 for a mass observed 4 weeks earlier. The pathologist reported a 'scirrhous carcinoma with metastases to axillary nodes." Received postoperative irradiation to involved side beginning May 8, 1937. Recurrences in scar removed May 1939 and September 1939. Metastases to left axilla and 6th thoracic vertebra appeared May 6, 1940, to left upper lobe on Sept. 12, 1940, and 2nd lumbar vertebra on Jan. 13, 1942. Herpes zoster also appeared, but date and distribution not stated. Died Aug. 7, 1943.

CASE 2. J.H., a 42 year old white female, had a left simple mastectomy performed Sept. 10, 1936 for a mass present 18 months. Received preoperative and postoperative Roentgen therapy, the latter including the opposite breast beginning Oct. 8, 1936. Pathologist reported "adenocarcinoma." On March 16, 1937 developed metastases to right ilium, 9th and 12th thoracic, and 2nd lumbar vertebra. Herpes zoster involving the left 1st lumbar distribution appeared Sept. 15, 1937. The sacrum, coccyx, and right acetabulum revealed metastases on Nov. 26, 1937. Died September 1939.

CASE 3. G.D., a 49 year old white female, had a left simple palliative mastectomy performed April 28, 1937 for a mass present for 11 months, together with supraclavicular adenopathy and skin nodules. Pathologist reported "adenocarcinoma." Received preoperative and postoperative Roentgen therapy, the latter including the opposite breast. Herpes zoster appeared in July 1937. Segments involved not reported. Generalized metastases on Sept. 17, 1938. Alive with malignancy when last seen on Dec. 17, 1938.

CASE 4. E.M., a 35 year old white female, had a right radical mastectomy performed Dec. 22, 1934 for a mass present 1 month. Pathologist reported "carcinoma with metastases to axillary nodes." Pre-operative Roentgen-ray therapy administered. Metastases noted in right ilium on Nov. 15, 1934, the 9th, 11th, and 12th thoracic vertebrae on November 2, 1935, and the odontoid on Aug. 29, 1936. Herpes zoster appeared on right side. Date and segments involved not stated. Died Oct. 22, 1936.

CASE 5. I. W. F., a 71 year old white female who was seen elsewhere for a mass in the right breast. No operation was performed, but Roentgen-ray therapy of unknown amount and factors was administered. Developed herpes zoster involving right 4th and 5th thoracic segments. Roentgen examination on Aug. 3, 1938 revealed metastatic disease involving the 5th thoracic vertebra. Died June 1939.

CASE 6. M. L., a 60 year old white female, had a left radical mastectomy performed June 16, 1939 for a mass which had been present for 2 years. The axilla was not completely dissected. Pathologist reported "adenocarcinoma with metastases to axillary nodes." No postoperative irradiation was administered. On Jan. 15, 1940, metastases developed in the left axilla and supraclavicular areas. On Sept. 8, 1942, metastases appeared in left internal mammary nodes and right breast. On Jan. 22, 1943, a bilateral pleural effusion and herpes zoster on the left side appeared. Segments involved by herpes not stated. Died July 27, 1943.

CASE 7. C.V., a 43 year old white female, had a right radical mastectomy performed Jan. 13, 1933 for a mass present 1 year. Pathologist reported "carcinoma with metastases to axillary nodes." Received postoperative Roentgen-ray therapy, including opposite breast. On Sept. 23, 1933, developed metastases to skin, right axilla, and possibly liver. Herpes zoster

involving right 7th and 9th intercostal nerves appeared, but date not noted. Died Dec. 14, 1933.

Case 8. R. T., a 45 year old white female, had a left radical and right simple mastectomy performed on April 19, 1935. Pathologist reported "carcinoma of left breast with lymph node metastases." Postoperative Roentgen therapy administered to both sides of chest beginning May 20, 1935. Herpes zoster appeared on left side on Oct. 28, 1936. Segments involved not stated. Pulmonary metastases noted Jan. 8, 1937. Died April 1937.

Case 9. C. G., a 57 year old white female, had a right radical mastectomy performed elsewhere on Nov. 15, 1932 for a mass present for 6 months. Pathologist reported "medullary carcinoma." Postoperative Roentgen therapy administered to both sides of chest beginning Jan. 4, 1933. Herpes zoster noted on right side in May 1934. Segments involved not stated. Died April 1935 with evidence of cerebral metastases.

Case 10. W. H. B., a 45 year old white female, had a right radical mastectomy performed elsewhere in May 1935 for a mass that had been present for 8 months. The pathological report was not available. Postoperative Roentgen-ray therapy was administered to both sides of the chest. Pulmonary metastases and recurrence in the scar appeared on Aug. 8, 1935. Herpes zoster was noted on April 28, 1936, the location and distribution being unspecified. Metastases appeared in the left breast on Oct. 30, 1936. Patient was last seen alive with malignancy on Oct. 30, 1936.

Case 11. L. J. H., a 75 year old white female, had a right radical mastectomy performed elsewhere in May 1932 for a mass present for 15 months. Postoperative Roentgen-ray therapy was not administered. A recurrence developed in the scar in February 1933. Herpes zoster appeared on the right chest on Sept. 6. 1933. Segments involved not stated. Internal mammary node metastases were noted on Jan. 3, 1934. Patient died March 22, 1935.

Case 12. E. L., a 75 year old white female, had a right radical mastectomy on Oct. 1, 1936 for a mass which had been present for 5 years. Pathologist reported "adenocarcinoma with lymph node metastases." Postoperative Roentgen therapy begun Nov. 4, 1936. Herpes zoster developed on right thoracic wall on March 24, 1937. Segments involved not stated. Died Sept. 21, 1938 with malignancy.

Case 13. R. S., a 74 year old white female, had a left simple mastectomy performed on May 15, 1935 for a mass present for several months. Pathologist reported "duct type of adenocarcinoma." Received postoperative Roentgen therapy, including opposite breast. Developed right herpes zoster facialis on Sept. 26, 1938. Alive and well on Dec. 6, 1944.

Case 14. D. A. H., a 64 year old white female, had a left radical mastectomy performed Nov. 15, 1932 for a mass present 3 months. Pathologist reported "scirrhous carcinoma." Postoperative Roentgen therapy to both sides of chest and left axilla begun Feb. 21, 1933. Developed herpes zoster on left side on June 8, 1934. Segments involved not stated. Died Nov. 17, 1941 of cerebral hemorrhage with no clinical evidence of metastatic disease.

Case 15. J. S., a 49 year old white female, had a left radical mastectomy performed on Aug. 12, 1932 for a lump which had been present 3 weeks. Pathologist reported "scirrhous carcinoma." Both sides of chest and left axilla were irradiated beginning Sept. 12, 1932. On Jan. 25, 1933 changes were observed in left lung which were believed to represent possible radiation fibrosis. On May 20, 1933 patient developed herpes zoster on left side. Segments involved not stated. Alive and well on April 26, 1945.

Case 16. W. R. T., a 74 year old white female, had a right simple mastectomy performed elsewhere on Aug. 1, 1937. Histologic examination revealed adenocarcinoma. Postoperative Roentgen therapy begun Feb. 28, 1938 to right breast and axillary region. Developed herpes zoster on March 7, 1938 on left side. Segments involved not stated. Alive and well on April 1, 1945.

**Comment.** Fourteen of the patients with herpes received preoperative or postoperative irradiation with Roentgen rays, or both, only 2 receiving no irradiation. All 4 of the patients who developed herpes without metastatic disease were subjected to irradiation. Of the latter 4, one developed facial herpes 39 months after irradiation of the breast and its lymphatic areas, whereas the other 3 developed thoracic herpes 40, 8, and 1 month respectively after irradiation. In view of the multiplicity of inciting agents, the possible etiologic rôle of irradiation must also be considered, although it is difficult to comprehend the significance of thoracic radiation in the production of facial herpes. In the 10 cases develop-

ing metastases who had postoperative irradiation, the possible etiologic rôles of both factors are to be considered. In only 6 of these cases was it possible to determine the time interval from irradiation to appearance of herpes, the figures ranging from 4 to 40 months.

Twelve of the cases of herpes developed evidence of metastatic disease either before or after the appearance of the eruption. Eleven of these cases had some type of breast operation performed. Of 350 cases operated upon, 218 (62%) subsequently showed evidence of recurrent or metastatic disease. Thus, the incidence of herpes zoster in metastatic disease was 11 cases in 218 (5.0%), while the incidence in those cases not showing metastatic disease was 4 cases in 132 (3.0%). Of 56 cases of breast carcinoma not subjected to surgery because of one or more contraindications, only 1 developed herpes zoster, and this case showed metastases.

The presence of metastatic disease was manifested clinically by supraclavicular nodes, cutaneous nodules, or rarely cerebral symptoms, while in others there was Roentgen evidence of pulmonary or bony involvement. All of these cases died at home, and unfortunately no autopsy studies are available. However, it is hoped that by calling attention to the relatively high incidence of herpes zoster in carcinoma of the breast this association will be noted more carefully in the future, and careful clinico-pathologic studies, particularly including that of the spinal cord, may reveal the etiological factors. Too often the lesions of herpes zoster are noted merely in passing, with no attention directed to the dermatomes involved and possible relationship to underlying neoplastic or inflammatory process.

Past evidence indicates that the metastatic disease merely prepares the soil *(terrain maladif)* for the invasion of the virus or causative agent of herpes zoster, rather than actually causing the disease itself. In some cases, knowledge of the association of herpes zoster and malignancy may aid in the uncovering of an otherwise cryptic neoplasm or unsuspected leukemia, although diagnosis rarely is a problem in breast carcinoma. All patients with herpes zoster should be subjected to a careful clinical study for possible neoplastic disease.

**Summary.** Herpes zoster occurs in relatively high incidence in carcinoma of the breast, especially in those cases showing metastatic disease.

Most of the patients developing herpes had been subjected to Roentgen radiation; the etiologic significance of radiation and metastases has not yet been clarified.

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## CURRENT TRENDS IN DIAGNOSIS AND TREATMENT OF CERVICAL CANCER

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RECENT years have witnessed a notable improvement in the diagnosis of early cervical cancer. A new disease entity[69,77], "noninvasive carcinoma" or "carcinoma in situ", has been established as the earliest known type of cervical cancer, and its detection has been made possible through the refinement of existing diagnostic techniques. These developments may be expected to produce a significant decrease in the 17,000 deaths caused annually by cervical carcinoma. Results of treatment have repeatedly shown that either irradiation or surgery can cure the majority of early cervical cancers; that neither can cure more than a discouragingly small percentage of moderately advanced cases; and that the real hope of improving survival rates lies in increasingly early recognition and treatment.

INTRAEPITHELIAL CARCINOMA. For many years cancer of the cervix was regarded as an invasive tumor only. Its intraepithelial stage was not recognized until 1933, when Schiller[69] published his historic paper introducing the concept of preinvasive cervical carcinoma—an intraepithelial surface cancer which he thought might be the beginning of the invasive tumor. To most pathologists Schiller's concept of a noninvasive cancer was a paradox. But evidence has gradually accumulated to confirm the malignant nature of the preinvasive lesion, so that now most gynecologists accept Schiller's hypothesis as an established fact[5,19,22,29,49,63]. The adjective "preinvasive" is not strictly accurate, and a more descriptive term such as, "intraepithelial" or "noninvasive cancer," or "carcinoma in situ" is more acceptable.

Sufficient data are now available for an accurate description of the disease: It is a preclinical stage of cancer and its diagnostic findings are histological. Microscopically, the cells have all the characteristics of invasive or metastatic carcinoma, but there is no invasion*; the cellular changes involve the full thickness of the epithelium; and the adjacent areas of cervical epithelium frequently show hyperactivity of the basal cell layer[5,22,29,62,63,69,77]. The cancer usually begins on the cervical portio at or near the mucocutaneous junction; the portio is almost always involved to a greater or lesser degree and the lesion may spread to the adjacent vaginal wall; endocervical involvement is present in more than half of cases and the endocervix may be the only area affected[19,49,63]. The lesion has no characteristic clinical appearance[19,22,63]. Intraepithelial cancers have frequently been found with benign lesions, but are being detected in grossly normal, asymptomatic cervices more and more frequently because of the widespread use of diagnostic screening methods[20,21]. Although carcinoma in situ is in itself asymptomatic, it has often been found in conjunction with lesions that cause irregular bleeding[19,22]. The average age of women with intraepithelial cancer is about 38 years- approximately 11 years less than that for patients with clinical invasive cancer[22,61,63]. The frequency with which it is being diagnosed is startling. Several investigators have reported an incidence of about 1%[14,20,21,22,61]. If this were confirmed we would have to accept the amazing fact that one woman in every hundred has a cervical cancer; this seems unlikely.

A number of clinically important problems concerning intraepithelial cancer remain unsolved. The first is the relationship of hyperactivity of the basal cell layer to the development of intraepithelial cancer. The pathologic appearance of the hyperactive cells suggests a premalignant lesion[22]. A smattering of clinical evidence is appearing to suggest that this altered activity may be precancerous, but proof is lacking[22].

Equally important is the relationship of intraepithelial to invasive cancer. An increasing number of instances are being reported in which invasive cancer has developed at intervals, varying up to 37 years[58], after an initial biopsy that showed carcinoma in situ**. Additional evidence that intraepithelial cancer is a stage in the pathogenesis of invasive cancer is the fact that complete study of some cervices that were found by random biopsy to harbor intraepithelial cancer have shown areas of invasion later[22]. These observations, together with the histologic picture, are sufficient evidence to indicate that noninvasive cancer is a stage in the pathogenesis of at least some invasive cancers. The percentage of untreated noninvasive cancers that will eventually become invasive has yet to be determined and there is no indication as to the percentage of clinically invasive cancers that were once intraepithelial cancers. It is probable that all intraepithelial lesions do not become clinical cancers and that all gross

* Pathologists differ in their use of the term "invasion"[19,22]. The most reasonable criteria, from a therapeutic point of view, would seem to be penetration of the basement membrane and invasion of the stroma[13,19]. But some include extension into the cervical glands without stromal involvement[22]. Additional disorder is caused by the fact that some investigators fail to exclude from their reports on intraepithelial cancer, cases of microscopically invasive cancers that were originally classified as intraepithelial but were proved to be invasive upon review. This confusion of terms and classification will lead to inaccurate statistics and possibly to improper therapy unless it is corrected.

** Galvin and Te Linde[22] collected 16 cases from reports of 7 investigators, added 1 of their own.

cervical carcinomas are not preceded by detectable intraepithelial malignant alterations.

Diagnosis. Since the earliest cervical carcinomas present neither signs nor symptoms, their detection depends entirely upon the application of laboratory methods of diagnosis. It is fortunate that practical techniques for detecting early cervical cancers have been perfected simultaneously with the establishment of criteria for their diagnosis. Although there is only one method by which the diagnosis of any cervical cancer can be confirmed—namely, cervical biopsy (knife cone biopsy with curettage)—there are 2 methods by which its presence may be suspected: random cervical biopsy and cytologic smear. The latter has been enthusiastically studied and developed since it was introduced by Papanicalaou in 1928[52]. The result is a voluminous literature which has established the value of the cytologic smear as a presumptive test but has neglected the difficulties of its practical application.

The technique[21,5153,55,56] by which a smear specimen is obtained and prepared for examination is simple (a specimen scraped from the portio, supplemented by one aspirated from the endocervix, provides the best sample[3,51]). Its study and interpretation, however, are difficult, time consuming, and require the skill of a specially trained cyto-pathologist[2,21,25,51,53,54]. It can detect an average of probably 90% of cervical cancers—different groups report variations in accuracy of from 70% to 99%—and false negatives are usually less than 5%[3,21,25,28,34,36,38,68,85]. As a screening method, overall accuracy is deceptively good, approaching 100%[25], because of the overwhelming number of benign and, therefore, correctly diagnosed, lesions composing the group.

The cytologic smear method has two advantages over biopsy: The first is the ease with which the specimen is obtained. This simplicity encourages its use[66]. The second is that the specimen is composed, at least theoretically, of samples from the complete epithelial surface of the cervix[57,66]. The complete coverage effected by the smear technique accounts for the increasing number of early cancers that are being detected by smear although missed by random biopsy[21,36]. This demonstrated ability and the advantages listed are the bases for the hypothesis that the vaginal smear is the better method for discovery of very early cancers[28].

At present, the practical use of the vaginal smear method for cancer detection is limited to the study of patients with cervical abnormalities or symptoms suggesting uterine disease; and to the screening of small groups of apparently normal women. The potential usefulness of the smear method as a screening technique is unlimited[20,21,62,67,68]; but the fulfillment of a program for regularly screening all women seems impossible when one considers the size of the task[18,25,60,87]. Since the main difficulty in such an undertaking is the time required for studying the smear specimens—usually estimated as 10 to 15 minutes[34]—the hope of accomplishing it appears to depend on further simplification of the method[2,24,60,87].

The chief disadvantage of cervical biopsy is its random character. A single biopsy will often miss a minute cancer or will depict a carcinoma as intraepithelial when in an adjacent area it may be invasive. Several modifications have recently been made in the technique of cervical biopsy to adapt the method to the detection and confirmation of early cancer. Multiple biopsies—excising two or more separated segments of cervix have been substituted for the single random or "office" biopsy. The value of each biopsy has been increased by a change in histologic interpretation—cancer

elsewhere in the cervix is suspected from the presence of abnormal basal cell hyperactivity in the biopsy. A random biopsy which shows intraepithelial cancer may, therefore, suggest hidden invasion; one which shows abnormal basal cell changes may point to a hidden or potential cancer; a negative biopsy may have missed a small carcinoma and its adjacent changes[22]. The deficiencies of random biopsy and the need for a method of confirming tiny cancers detected by the smear technique[4] have led to development of the most accurate method of diagnosing cervical cancer: the knife cone biopsy combined with endocervical curettage. Since this is a supplementary technique which requires study of additional cervical tissue, the random biopsy or smear should be reported before cauterization or electrocoagulation of the cervix is allowed to destroy the cellular morphology of the area under consideration[1]. The endocervix is curetted, following which the cervical portio and mucocutaneous junction are completely excised. Study of this tissue affords unequivocal proof of the presence or absence of cervical cancer. It should be employed not only in cases requiring complete cervical study but as a screening method for all gynecological patients who are operated upon without removal of the cervix. Similar laboratory study is indicated for all cervices that are removed incidentally at operation, because they may contain unrecognized cancer.

If "suspicious" biopsies are followed by knife cone biopsies, it is probable that the combined study will detect almost all cases of cervical cancer. It is not difficult to take a random biopsy in the office. Combining the two forms of biopsy seems practical, therefore, for both the clinician and pathologist and may be useful as a screening technique[12,30]. Cox *et al.*[12] in a study of 171 cases demonstrated the effectiveness of the method. They found 7 suspicious cases by random biopsy, of which 3 proved to be intraepithelial cancers and 2 early invasive carcinomas by the use of knife cone biopsy. A similar routine has been employed at this hospital for some years and, as far as is known, no cancer has been missed: 36 cases were diagnosed as carcinoma in situ by an original biopsy, but complete study[58] showed invasion in 18.

It is apparent that the 2 methods by which early cervical cancer can be detected—smear and biopsy—have identical aims and indications. Although the accuracy and practicality of each method varies, either can detect the great majority of cancers[25]. They are not competitive methods. When both can be employed, the combination increases accuracy and is, therefore, the ideal method of cancer detection[3,21,28]. When only one is available or practical in a given instance, it should be used confidently but with an awareness of its limitations—namely, that it may miss cancer and that, when the vaginal smear method is employed, a positive report must be confirmed by microscopic study of sufficient cervical tissue.

TREATMENT. With the improvement in diagnostic techniques, more and more cases of early cervical cancer are being discovered. Some are intraepithelial carcinomas, for which there is no precedent for treatment. Others are early invasive cancers, most of which would have been treated in the past with Roentgen rays and radium. However, dissatisfaction with the imperfect results of irradiation and the need for a method by which to treat noninvasive cancers have caused some gynecologists to re-explore surgery as a method for treatment of cervical carcinoma.

Because carcinoma in situ is a localized lesion, it is best suited for surgical

excision. Assuming that invasion is absent, total hysterectomy with excision of a small cuff of vaginal epithelium should cure 100% of cases. Although trachelectomy may cure some surface cancers, the malignant nature of the lesion and the undiscernible extent of its spread indicate the need for a more radical type of operation to assure complete excision of the carcinoma[19,63]. Conservation of an ovary is probably permissible if the patient is young[19,22]. To the operative method just described, Te Linde and Galvin[77] have added parametrial excision, because of the frequency with which microscopic malignant invasion is found by study of the cervices after their removal. This addition increases the hazard of operation because it requires ureteral dissection. Employment of knife cone biopsy will permit proof of the presence or absence of invasion before final treatment[12,19,21,46]. If invasion is absent, the more radical procedure is unnecessary; if it is present, although only microscopically, disregard of lymph node metastasis would seem unwise. Excision of lymph nodes is an essential part of the surgical attack on invasive cervical cancer.

Two types of operations for invasive cancer are being investigated in the present surgical revival: the so-called Wertheim operation[10] and the regional lymphadenectomy of Taussig[75]. The former includes a group of operations in which total hysterectomy and bilateral salpingo-oophorectomy are combined with the removal of various amounts of the vagina, parametria, cul-de-sac, and regional lymph nodes[8,41]. Regional lymphadenectomy, when employed as the only surgery, is always combined with irradiation therapy and is designed to remove the pelvic nodes to which cervical cancer metastasizes: the ureteral, iliac, obturator, and hypogastric groups[74].

The surgical experiment has been in progress for so short a time that complete results will not be available for some years. However, we can reach certain tentative conclusions and we can define the problems that any re-examination of surgery must answer.

To date, the important conclusion is that radical surgery can now be performed safely in carefully selected cases by skillful gynecological surgeons trained in the technique of the operation. Meigs[42], who employs surgery in 10% to 15% of cases, has reported 91 Wertheim type operations without a surgical death. Although this record has not been duplicated, it is probable that the operation can be performed in selected early cases, comprising possibly ¼ of all cervical cancers, with an operative mortality of no more than 5%[8,17,64]. Brunschwig[9] is demonstrating that extremely radical surgery—complete excision of the pelvic viscera—can be done with a low surgical mortality rate in advanced cases with the help of good modern pre-operative and post-operative care. Meanwhile, Taussig[75] and Morton[44] have demonstrated the safety of regional lymphadenectomy, and Nathanson and Parsons[57] have developed an extraperitoneal approach for removal of regional nodes which is equally complete and may prove to be safer than the transperitoneal approach. The most frequent serious complication of radical pelvic surgery – ureteral fistula – has been almost eliminated by preservation of the ureteral blood supply[42,43]. Because the mortality rate of irradiation is admittedly lower than that of surgery[23,73], results showing the safety of surgery are an encouragement for the continuation of the experiment rather than an argument in favor of surgical treatment.

One undeniable indication for excising a cervical cancer is the presence of a radioresistant tumor. The frequency of this tumor type is uncertain; it has

been described as uncommon[11,71] and has been estimated as high as 50%[26,27]. It can be recognized clinically by observing the response of the neoplasm to irradiation, but this is unsatisfactory, because by the time an unfavorable response is confirmed, the lesion may be inoperable or the patient may have become a poor surgical risk. Several investigators suggest that radioresistance can be detected preclinically by study of vaginal smears or biopsies taken during irradiation therapy[26,27,82]. If this is confirmed a method will be available for scientific segregation of a group of cervical cancers which cannot be cured by irradiation and for which radical surgery is the only recourse.

Radioresistance of metastatic cancer in lymph nodes is frequently proposed as an indication for Wertheim type operation or regional lymphadenectomy following irradiation[11,26,64,71,74,75]. The degree to which these lesions are radioresistant is uncertain. Past clinical experience suggested that irradiation rarely if ever destroyed cancer in nodes[6,40,46,64,74], but more recent evidence indicates that it does, at least, in some cases[45,64]. If modern irradiation can destroy cancer in lymph nodes as frequently as surgery, one of the main and historic arguments for the surgical treatment of cervical cancer is defeated[64]. It will be important, therefore, to determine how frequently modern irradiation can destroy metastatic cancer, since surgery can eradicate proved lymph node metastasis in only 20% of patients[6,64,74,75]. The present re-examination of surgery should answer this question and should determine whether lymph node metastasis is or is not an indication for the operative removal of the nodes. Meanwhile, the determination of the radioresistance of tumors is of practical value in determining which patients may be benefited by regional lymphadenectomy: salvage cannot be increased by lymph node excision if the primary tumor is both radioresistant and inoperable[26].

The argument is sometimes put forward that curative surgery results in lower morbidity and fewer complications in early cancer than curative irradiation. However, the question is not one that lends itself to statistical analysis[14]. Clinicians who have had to treat a significant number of severe post-irradiation reactions may favor surgery. Those who have been plagued by surgical patients complaining of severe bowel, bladder, and ureteral injuries or a functionless, short vagina may favor irradiation. It has been proved that good results with few complications can be obtained by good surgery performed upon carefully chosen patients[42]. But this is also true of irradiation therapy, particularly in a similarly selected group treated carefully by a competent therapist[35]. Many of the complications of irradiation therapy are due to overtreatment resulting from the combined use of radium and Roentgen rays[46,71]. There is recent evidence that early cases do not require Roentgen-ray treatment in conjunction with radium, and the elimination of Roentgen rays from the therapy of these early cases may reduce the number of complications[78]. The frequency and severity of therapeutic complications that follow various techniques of treatment with similar salvage rates depends more upon the judgment, experience, and ability of the therapist than upon the method of treatment which he uses.

Since inadequate irradiation therapy is followed by poor results, pre-existing complications which might prevent complete treatment may be important indications for surgery. Among these are certain cases of pelvic inflammatory disease, endometriosis with hematomata, vaginal stenosis, pelvic tumors, pregnancy, emotional disturbances, and

lack of cooperation on the part of the patient[11,64].

It has been suggested that "cure" of cervical cancer by surgery is more permanent than that by Roentgen rays[6,41,64,74]. Garcia and Melville[23] concluded from a study of cases in the literature, that this hypothesis is unproved. The premise that excision of the malignant cervix will improve survival rates by preventing local recurrences and the development of new cervical cancers seems equally questionable[11,35,72].

The major part of this discussion of therapy has been allotted to the surgical method because the revival of surgical excision is still new and experimental and, therefore, of particular interest. Surgery may be expected to play an increasingly important role, particularly in the recently expanding field of early cancer. Irradiation, however, maintains undisputed supremacy as the treatment of choice for most cases of cervical cancer. New developments, and the lessons learned from experience, are making irradiation safer and more cancerocidal. Probably the most important advance in irradiation therapy has been establishment and application of the concept of tissue tumor dosage[23,37,47,48,50,79,83,86]. By calculating the irradiation which each tumor, its metastases, and the surrounding normal tissue receives, the therapist can assure the greatest, safe dose of irradiation to each cancer. This feature is but a part of an important trend to individualize irradiation treatment rather than to apply it as an inflexible and preconceived pattern to every patient. It also includes variations in therapy required by incidental complications such as debility, sepsis, and anemia[7,11,32,35,59]. Completion of a curative course of irradiation may be possible only after these modifying factors have been corrected. Results are further improved by a more precise application of therapeutic technique[11,15,16,23,31,32,35,84], for instance, roentgenologic determination of radium placement[33,37,81]; the development of new therapeutic methods[35,37,65,76,80,82]; and the prompt recognition and treatment of therapeutic complications[23,31,71].

**Results.** The best method of determining the value of treatment methods is the analysis of their salvage rates. Final evaluation of the modern surgical experiment must await a longer period of observation. Predictions based upon past surgical experience are uncertain and might cause undeserved prejudices. Past surgical results have not equalled those of irradiation; surgery has effected a 5 year "cure" in less than 70% of early invasive cases. Surgical success will always be limited by distant nodal metastasis—not uncommon even in early cases—and by the inevitable incompleteness of the lymph node excision[49,64,71]. Preliminary observations of the recent surgical experiment suggest, however, that safe radical surgery may attain a cure rate comparable to that of irradiation and, in certain instances, will cure patients who would otherwise die. Experience with the combined use of lymphadenectomy and irradiation suggests that it, too, may improve the chances of survival in some cases[26,35,44,45,64,74,75]. The best cure rate which has been proved has been obtained by irradiation therapy. The absolute 5 year salvage of all cases treated by irradiation averaged 35% in a recent collective review; that of Stage I cases was 73% and a number of investigators reported a survival rate of more than 80%[14,23,39,70].

**Comment.** In conclusion it may be said that irradiation therapy remains the treatment of choice for most patients with cervical cancer; that results of irradiation may be favorably influenced by the addition of regional lymphadenectomy; that radical surgery

can be done safely and has an increasingly important place in treatment of early cancers, particularly of the noninvasive type, and possibly in selected groups of invasive cancer; and that individualized therapy, is the best method of curing the greatest number of patients and, at the same time, assuring their comfort and happiness.

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# PEDIATRICS

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## THE PHOSPHATASES IN RELATION TO CLINICAL PEDIATRICS

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THE PHOSPHATASES partake in the dynamic equilibria of the body economy by breaking down enzymatically the organic esters of phosphoric acid. They enter actively into the intracellular hydrolysis of organic phosphates of all sorts, including the phospholipids, phosphoproteins, nucleotides, and phosphorylated carbohydrates. They appear to be omnipresent in nearly every tissue of the body. They are also demonstrable in the circulating blood, in concentrations which may become increased or decreased in certain disease states. Studies of their concentration in the circulation have proved of practical diagnostic significance, even though the causative mechanism of these changes is far from adequately elucidated.

The phosphatases are usually separable into 3 main groups: phosphomonesterases, phosphodiesterases and pyrophosphatases. Separation of one from another is based fundamentally upon the molecular architecture of the phosphatic substrates used in the testing for these enzymes. Some appear to be highly specific, such as choline phosphatase, ribonuclease, thymonucleodepolymerase, and 5-nucleotidase. The phosphomonesterases are the variety ordinarily found in the blood stream, and will receive chief attention in this Review. In the ensuing text the term phosphatase is used as an abbreviation for phosphomonesterase, unless otherwise stated. The symbol AP is used for "alkaline phosphatase," and SAP for "serum alkaline phosphatase."

TYPES OF PHOSPHATASE. Folley and Kay[32] have described 3 types of phosphomonesterases which may be found within human tissues. There are the alkaline phosphatases with a range of activity from about pH 6.0 to 10.0 and a pH optimum between 9.0 to 10.0. These occur in bones, kidneys, liver, intestines, mammary glands, lungs, blood plasma, and miscellaneous other sites. A second type is the acid phosphatases, with a pH optimum of 4.5 to 5.0, found to some extent in the spleen, liver, pancreas and kidney, and to an unusual degree within the prostate. A third phosphatase, also called an acid phosphatase, has been demonstrated in the erythocytes. This has a pH optimum of approximately 5.3, and appears to differ in certain properties from the other acid phosphatases.

Many attempts have been made to differentiate these enzymes in the various tissues from each other, but

without much success. It is probable that the phosphomonoesterases are not highly specific and that they will attack a large variety of organic monophosphates.

Most of the phosphatases are highly sensitive to changes in hydrogen ion concentration and can be activated by magnesium salts. Many activators and inhibitors have been uncovered by the biochemists, but this aspect of their chemistry is beyond the scope of this discussion. In clinical testing all the variables are standardized with the exception of the content of enzyme free in the blood plasma. Good reviews on the chemistry of the phosphatases and their substrates can be found in the reports by Folley and Kay[32], Moog[69].

Chemical Structure. The actual chemical structures of the different phosphatases are not known. They all appear to have a complex proteinous structure, with molecular weights ranging from 6,000 to 10,000. Considerable work has been done which shows apparently significant differences in the alkaline phosphatases from different sources but thoroughly purified preparations will be needed before the uncertainties regarding the nature and chemical identity of the phosphatases can be resolved.

Physiological Significance. The roles played by the phosphatases within the body economy seem to depend largely on where they are situated within the body. The functions which have attracted widest interest are those concerned with absorption of food from the gastrointestinal tract, dephosphorylation within the liver, reabsorption of glucose by the kidney tubules, and deposition of lime salts within the bones.

Gastro-Intestinal Tract. In gastrointestinal absorption, the glycerol from the fats is first linked with a phosphate ion through the mediation of a phosphorylase to form glycerophosphoric acid which is then hydrolyzed by AP and the glycerol absorbed. AP also takes part in the synthesis of lecithin from phosphotidic acid and choline and in the formation of a diglyceride from lecithin. Prolonged fat feeding results in an increased SAP which presumably is of intestinal origin. AP is also concerned with nucleoprotein metabolism and catalyzes the hydrolysis of mononucleotides to nucleosides and phosphate. The nucleosides may then be absorbed directly or be hydrolyzed to purines and carbohydrates with the aid of purine nucleosidase and then absorbed. AP also liberates phosphoric acid from phosphoserine and from peptones containing this ester.

In gastro-intestinal carbohydrate absorption, both glucose and galactose, and fructose to a lesser extent, are converted to phosphoric esters in the mucosa by phosphorylase. These esters are subsequently hydrolyzed by AP and the liberated monosaccharides enter the portal blood stream. Alimentary hyperglycemia results in increased SAP.

Kidney. Within the kidney tubules the glucose which dialyzes through the glomeruli is first phosphorylated in the course of tubular reabsorption by the kidney phosphorylase[29]. AP hydrolyzes this ester so that the glucose can be returned to the blood stream. Wilmer[99] believes that there is a direct correlation between the functional activity of the renal tubule and its AP activity.

Bone. AP occurs abundantly in embryonic bone and ossifying cartilage and in osteoid tissue which ultimately will become bone, but not in cartilage of the non-ossifying type. It is also present in teeth. The enzyme is usually though not invariably associated with the tissues in which hard structures are being abnormally formed[69].

The explanation for calcification is much more complicated than being simply a chemical precipitation of calcium and phosphorus as a consequence of the presence of AP in some quantity in certain tissues[32,69]. AP is present in organs which do not normally calcify, such as intestinal mucosa, liver, mammary glands and kidney. Furthermore, in rickets, calcification is arrested although AP is present in abundance in the osteoid tissue near the zone of provisional calcification.

Bone and tooth formation are believed to require a "second" or "inorganic" mechanism. It has been postulated that AP acts on the different gluco phosphoric esters to produce carbohydrate breakdown products and phosphate ions. The phosphate ions then combine with calcium ions until the solubility product of calcium phosphate is exceeded and calcium phosphate is precipitated into the matrix of the bone[12].

Excretion. AP is excreted in the feces and to some extent in the urine. Burgen[22] measured urinary AP and found it to be scanty and irregular with no variation with age and sex. Lawrie[61] has found that a normal adult excretes an average of 23.0 units of alkaline phosphatase (Bodansky method) per gm. dry weight of feces. This presumably is derived from the waste AP from the bile, succus entericus, and others.

Alkaline Phosphatase in Tissues. *Methods*: Determination of AP in tissues can be done either by chemical extraction or histologic staining. Most tissues contain both acid and alkaline phosphatase. Extractions are performed by grinding and macerating a known quantity of the tissue and then autolyzing the mixture for a variable period of time in water or chloroform-water. The mixture is then filtered and the enzyme activity of the filtrate is determined by one of the methods used in the measurement of SAP. Drabkin[29] has found that homogenization of the powdered tissues will yield much higher activity values.

The enzyme was demonstrated histologically simultaneously in 1939 by Gomori[39] and Takamatsu[86]. One imbeds the tissue in paraffin, cuts and mounts the section on a glass slide and then allows the AP of the particular tissue to act on a substrate of sodium glycerophosphate and calcium nitrate. The glycerophosphate is hydrolyzed and the liberated phosphate ion joins the calcium ion until the solubility product is exceeded and the calcium phosphate is precipitated *in situ*. The calcium phosphate is then changed to a visible form either by reacting with added silver nitrate to form brown to black silver phosphate or by reacting with cobaltous nitrate to form cobalt phosphate which is subsequently converted to black cobalt sulfide by the addition of ammonium sulfide. The tissue may then be counterstained. Menten *et al.*[68] have described a histochemical azo dye test for kidney AP which is said to give results comparable to those of Gomori and Takamatsu. Other modifications have been likewise proposed.

Many variables are inherent in both the tissue extraction and the tissue visibility methods. Aside from maintaining precise control of pH and temperature, one must deal with many inherent difficulties such as magnesium ion content, and others. Williams[98] has stated that phosphatase may be activated as much as 5,000% by the proper concentration of magnesium ions.

Few successful attempts have been made to correlate SAP and tissue AP quantitatively, though it is well known that in diseases of either bone or liver both the SAP and tissue AP may become elevated.

*Bone*. AP is found in nearly all grow-

ing and ossifying bone. In stained preparations it is most abundant in the osteoblasts and proliferating cartilage cells of the epiphyseal portions of the bone and in the cells of the inner layer of periosteum in the metaphysis. Most of the studies on bone have been chemical in nature, for it was not until comparatively recently that Barger[5] and Lorch[62] perfected the technic for the histochemical demonstration of the enzyme in bone.

Woodard[101] has demonstrated that the average AP content of the cortex of adult bone is between 0.04 and 0.15 units per gm. (Bodansky method) while that of children's bones is between 0.16 and 3.3 units per gm. Acid phosphatase activity in normal bone was barely detectable. Regenerating bone may have up to 50 times the AP content of normal bone. Bakwin and Bodansky[3] found the AP increased in the bone in rickets, fragilitas ossium, osteitis fibrosa, osteomalacia, osteitis deformans and hyperthyroidism.

*Digestive System.* Berliner[10] has shown the tooth buds of the fullterm fetus to be strongly positive for AP. There was no appreciable enzyme activity in adult teeth. Provissimato[72] had stated that the AP of adult teeth increased in dental caries and pyorrhea but this was not verified by Berliner. AP has been found in saliva and in the salivary gland. The problem of the origin of the salivary AP is not wholly solved. Smith[82] stated that it probably came from the desquamated gingival epithelium. However, both Zander[104] and Glock[38] after extensive studies decided that it was probably of bacterial origin, inasmuch as AP has been found in some bacteria. Bray[20] has suggested taxonomic classification of the Corynebacteria on the basis of the AP reaction.

The superficial and occasionally the deep cells of the filiform papillae of the tongue give a positive AP reaction. The epithelial cells of the gastric mucosa are uniformly negative for AP. AP has been demonstrated in all portions of the mucosa of the small intestine. Koster[59] found a decrease in the intestinal excretion of AP in nontropical sprue and Heymann[47] noted decreased excretion of the enzyme in rickets, spasmophilia and intestinal infantilism. Kosmann[58] found the AP of the small intestine increased after a fat or protein meal and somewhat after a carbohydrate meal. He estimated that the AP was highest in the duodenum and lowest in the ileum. The large intestine has been universally negative for AP except for some positive capillaries. Kabat and Furth[52] found no AP activity in the human pancreas, but the islets of Langerhans are rich in acid phosphatase[70].

*Liver.* The distribution of AP in the human liver was studied thoroughly by Wachstein and Zak[96], who found that normally the cytoplasm of the hepatic cells reacted with only a faint and uneven AP stain. The nuclei, including the chromatin, nucleoli and nuclear membrane, were markedly positive. There was a varying degree of AP in the sinusoidal walls and the Kupffer cells and also in the nuclei of the bile duct epithelium. The endothelium of the larger veins, small arteries and arterioles showed great AP activity while the staining of the bile capillaries was variable. The liver seems to have a higher content of AP than of acid phosphatase, whereas in kidney and blood plasma the reverse is true[29]. The findings with respect to the liver are different in different animal species.

Many studies have been done on the alterations of hepatic AP in the liver diseases. Gad[35] found that AP increased in the dogs liver after ligation of the common bile duct. Wachstein and Zak[96] substantiated this and found the enzyme activity prominent chiefly in the bile capillaries. The AP became

progressively increased with the duration of the obstruction. Wachstein[95] found that the AP in human obstructive jaundice increased markedly in the bile capillaries with little or no increase in the hepatic cell cytoplasm. He noted that the sprouts of biliary proliferation showed no particular enzyme activity. Sherlock and Walshe[80] found an increase of AP in obstructive jaundice throughout all parts of the liver except in the connective tissue.

In liver necrosis Wachstein[95] found no appreciable increase of AP in the degenerating liver cells. The bile capillaries were devoid of the enzyme whereas the proliferating fibroblasts and lymphocytes showed a markedly positive reaction. In hepatic cirrhosis the AP was normal in the undamaged cells and showed no increase in the necrotic cells. There was a variable increase in AP in the bile capillaries and in the connective tissues. Sherlock and Walshe[80] found a variable AP increase in the hepatic cells, and bile canaliculi in hepatic cirrhosis and a definite increase of the enzyme in the sinusoidal and connective tissue. There was a general decrease in the AP in fatty livers. In acute hepatitis Sherlock and Walshe[80] found an increased AP in the hepatic cells sinusoidal walls and portal tract. Thannhauser[90] found decreased AP in the liver in Von Gierke's disease.

*Urogenital System.* The AP in the kidney is located chiefly in the upper part of the proximal convoluted tubules and to a lesser extent in the lower portions. No AP is seen in the distal convoluted tubules, the loops of Henle, the collecting tubules or in the glomeruli (except in the cat). The smaller renal vessels are usually positive. AP has also been found deep in the transitional epithelium of the urinary bladder. In experimental hydronephrosis of animals the renal AP often shows appreciable diminution[99]. There is a high content of acid phosphatase in the prostatic epithelium.

AP has been demonstrated in the endometrium and to some extent in the circular muscle layer of the myometrium. Dempsey and Wislocki[28] state that the placenta of the sow, cat, guinea pig and human all contain phosphatases which will split fructose diphosphate, glycerophosphate, lecithin and yeast nucleic acid.

Gomori[40] demonstrated the presence of AP in the lining of the seminiferous tubules and in the epididymis. Macleod and Summerson[63] state that AP is present in the sperm. Furth and Kabat[52] showed it to be present in the spermatogenic cells and basement membrane of the testes. Hexosediphosphatase is present in the nuclei of the human vas deferens[105].

*Blood and Vascular System.* There is considerable variability of AP content, depending on the organ and species but in general one usually finds a rich deposit in the capillaries, arterioles and venules. Zorzoli and Stowell[105] have found hexosediphosphatase in the intima of the human aorta.

AP activity in the blood and bone marrow cells have been studied by Wachstein[95]. Normally the erythrocytes, lymphocytes, monocytes, eosinophils show no AP, whereas the neutrophils show variable AP. Similarly, in the bone marrow, AP was seen only in the neutrophils of the myeloid series and occasionally in the nucleated red cells, erythroblasts. The principal phosphatase in the erythrocytes was shown by Behrendt[9] to be one with maximal activity at pH of 4.8 to 6.1 (see later discussion).

In the pyogenic infections neutrophils have an increased AP content, particularly in the cytoplasm[95,31]. Patients with infectious mononucleosis or eosinophilia had no increase of AP in these cells.

*Spleen.* Davis[27] first found AP in the

splenic extracts. Bourne[18] found the contents to be in the Malphigian corpuscles and lymphocytes. Kabat and Furth[52], Gomori[40] and Greenstein *et al.*[42] found AP only in the endothelial elements.

*Lymph Nodes.* According to Kabat and Furth[52] only the endothelial cells of the blood vessel walls are positive for AP. Gomori[40] lists the lymph nodes as having a variable AP content.

*Nervous System.* The AP content of the brain seems to be based on the degree of vascularity, inasmuch as AP is stainable only in the endothelium of the blood vessels in the central nervous system[60].

*Respiratory System.* Kabat and Furth[52] and Gomori[40] found a positive reaction in the brush borders and the submucosal glands of the trachea and bronchi. There was an occasionally questionable AP reaction in the alveolar septa of the lung and a more or less uniformly positive reaction in the pulmonary capillaries.

*Endocrine System.* AP has been found in the adrenal cortex but not in the medulla[40], and especially in the zona reticularis[52]. The capillaries are also positive. In the thyroid, AP is found only in the capillaries[40,52]. Gomori[40] was unable to demonstrate AP in the parathyroid. In the pituitary, AP is seen in the neurogenic cells of the posterior lobe, the capsule and the capillaries but not in the anterior lobe[52].

*Miscellaneous.* Muscle is uniformly negative except for the capillaries. The content of AP in the skin is variable. Wilmer[99] was unable to demonstrate the enzyme in the inclusion bodies of vaccinia, herpes simplex, fowl pox or tracheolaryngitis.

*Neoplasms.* Research into the AP content of neoplastic tissue is comparatively new. Landow and associates[60] studied AP in central nervous system neoplasms and found it in the meningiomas but absent in the astrocytomas, oligodendromas and glioblastomas. Woodard and Higinbotham[100] found the AP content of osteogenic sarcomas highly variable with no correlation with the histologic structure. Benign osteochrondromas and giant cell tumors showed no enzyme activity, while malignant giant cell tumors tended to be positive. Embryonal adenomas of the testes[100] and also thymomas[42] contained AP, whereas malignant epitheliomas, carcinomas of the breast, liposarcoma, malignant melanoma, adamantinoma and hypernephroma did not[52]. Fibroadenomas of the breast showed some AP in the ducts. Carcinomas of the intestine were questionably positive[52]. Wilm's tumor has exhibited a moderate amount of AP particularly in the stroma[52]. The cells of acute myeloblastic leukemia had no increase in AP and perhaps actually showed some decrease compared to those of the normal person[95]. Those of chronic leukemia were consistently negative[95]. Kabat and Furth[52] could find no AP in the cells of acute lymphatic leukemia. A range of AP activity from 0 to 115 units per gm. (Bodansky method) has been found in extracts of osteogenic sarcoma tissue by Woodard[101]. No correlation was found between phosphatase activity and histologic structure of the tumors. Soft-part metastases from osteogenic sarcoma had AP activities of the same order of magnitude as the primary tumor. The phosphatase of extracts of giant cell tumors and of endothelioma of bone were active mainly in acid solution.

Acid Phosphatase in Erythrocytes. The acid phosphatase in human erythrocytes is distinctly different from the acid phosphatase which occurs in the blood plasma normally or the (probably) other variety which appears in the plasma of patients with metastasizing cancer of the prostate

Studies by Sullivan, Gutman and Gutman[85], Behrendt[9], and King, Wood and Delory[56], have confirmed the individuality of this phosphatase. It has a strong activity in the range between pH 4.8 and pH 6.1, with an optimum at about pH 5.3. Curiously, its action upon B-glycerophosphate is slow compared to a much stronger activity against the phenol phosphates. It displays little activity against the phosphoric esters of alcohols, glycerol and hexoses. With phenolphosphate as substrate, King and Armstrong found the values in normal persons to be from 200 to 400 units per 100 cc. with an average of 340 units[55]. They failed to discover any abnormality in disease states. These figures were secured by determinations made from blood cells laked with distilled water. The cells were washed and subsequently hemolyzed.

Behrendt has recently reported studies made on whole blood, blood plasma, hemolyzed erythrocytes and suspensions of erythrocytes in saline solutions[9]. When the phosphatase activity of hemolyzed cells was compared with plasma phosphatase from the same blood sample it was noted that the phosphatase activity of the red cells of pH 8.9 in terms of units was more than twice as great as that of the plasma, whereas at pH 4.9 the red cells possessed an activity at least a hundredfold that of plasma. Behrendt's averages for the acid red cell phosphatase was between 94.4 and 305.3 Bodansky units, with an average of 159.1 units. These values were somewhat lower than those of King and Armstrong. Experiments with whole blood revealed that the hydrolytic effect upon buffered phenolphosphate was almost as strong as that of laked erythrocytes when the blood was prevented from being hemolyzed during the testing period. The acid phosphatase activity of the red cells proved to be lower when they were suspended in plasma than when suspended in saline solution. Inasmuch as washings of these red cells were free of enzymatic activity, it was evident that at pH 4.9, phenolphosphate must penetrate through the red cell membrane in order to be acted upon by the contained phosphatase. Rustbrunner[77] states that the acid phosphatase of the erythrocytes when measured at pH 6.8-7.0 fluctuates with age. There is an increased phosphatase in the erythrocytes of the newborn which subsequently decreases and then later increases in old age.

Serum Phosphatase Levels. Tests for the content of the phosphatases in the circulating blood have been performed in almost every kind of illness and hundreds of studies recorded. Most of the methods of blood analysis determine and express the content of AP in terms of measurements per unit volume of serum, despite the fact that within the body the circulating enzyme is in plasma rather than serum.

The presence of the phosphatases within the circulation is believed to result from overflow from the organs where the enzyme occurs in large amounts, chiefly liver, kidneys and bone, rather than indicating physiologic functional activity upon the constituents of the blood itself. The phosphatase contained within the red cells may be an exception. According to this interpretation, an elevated plasma content of either alkaline or acid phosphatase represents either a lack of balance between leakage into the circulation and excretion by the kidney and liver, or else a continuously greater current of the enzyme from site of origin to site of excretion. Much still remains to be learned about the metabolic cycle of the phosphatases.

Because the phosphomonoesterases

are not highly specific for single substrates, it is possible to utilize any one of a number of simple phosphatases as substrates for clinical testing. The Bodansky method measures, under standardized conditions, the liberation of inorganic phosphates from B-glycerophosphate[16]. One Bodansky unit is defined as that amount of enzyme in 100 cc. of plasma which will liberate 1 mg. of phosphorus (as the phosphate ion) during the first hour of incubation under the conditions described. With the Kay or Jenner-Kay method, one unit represents the liberation of 1 mg. of phosphorus as free phosphate from an excess of disodium B-glycerophosphate at pH 8.8 in 3 hours when kept at a temperature of 37.5 C.[53,54]. The King-Armstrong method utilizes disodium phenylphosphate as substrate and measures the phenol in 30 minutes under the conditions of the test. Several later simplifications of the King-Armstrong technic have found acceptance in many laboratories. It is estimated that one Jenner-Kay unit equals approximately 2 Bodansky units. One King-Armstrong unit is approximately equivalent to one Jenner-Kay unit. Huggins and Talalay[49] have proposed sodium phenolphthalein phosphate as buffer with colorimetric readings of liberated phenolphthalein as the index of enzyme activity. To escape from the need for venipuncture demanded by the above methods, Bessey, Lowry and Brock[11] have developed a micromethod which can be done on fingertip blood. This employs paranitrophenyl phosphate as the substrate, and the results are expressed in nitrophenol units. One nitrophenol unit is approximately equivalent to 1.79 Bodansky units.

The technics of testing for the acid phosphatases are much the same as for the alkaline variety except that different buffers are employed in order to obtain the desired acid pH of the environment.

Because of the diversity of methods in clinical practice, it is especially important to know which procedure is being employed by the laboratory whose services are being utilized, and what the limits of normality are, not only for that particular procedure but for that individual laboratory as well.

Serum Acid Phosphatase. A small amount of acid phosphatase can ordinarily be demonstrated in the serum of every person, regardless of age or sex. An elevation in serum acid phosphatase is almost never seen except in carcinoma of the prostate which has broken through its capsule to invade the periprostatic tissue or metastasize distantly to bone. The source of the increased serum acid phosphatase in such malignancies is clearly the prostatic epithelium itself or the cancerous epithelioma derived from it. McWhirter[67] has described slight elevation in serum acid phosphatase in ankylosing spondylitis of males.

The production of acid phosphatase by the prostate is influenced to a large extent by gonadal activity. It does not appear in any quantity until adolescence is attained, and the amount produced can be increased by giving of androgens or decreased by giving estrogens.

Large quantities of acid phosphatase are present in adult semen. The origin of this enzyme seems to largely lie in the prostate. Prostatic fluid obtained by massage is rich in this enzyme, whereas the other secretions which combine to make up the ejaculate do not contain any and in aspermia the ejaculates have phosphatase values as high as ejaculates containing spermatoza. No other body fluid contains acid phosphatase in anywhere near the concentration reached in the seminal fluid (apart from the blood in carcinoma of the prostate). Riisfeldt[75] has applied this knowledge to the medico-legal problem

of proving or disproving the presence of semen in dried spots on clothing. The recovery of large amounts of acid phosphatase, from such spots, is presumptive identifying evidence when an accusation of rape has been made.

Serum Alkaline Phosphatase. Generally speaking, the SAP level is elevated in osteogenic sarcoma, rickets, osteomalacia, generalized osteitis itis fibrosa cystica, osteitis deformans (Pagets' disease), pregnancy (especially the last months), secondary carcinoma of bone, infectious mononucleosis, idiopathic steatorrhea, and jaundice[81]. A SAP increase, therefore, cannot be interpreted as being diagnostic or even indicative of any one disturbance, in the absence of other pertinent information regarding the patient.

Alkaline Phosphatase. The origin and excretion of the circulating SAP is far from settled. Armstrong and Banting[2] suggested that the osseous system is the origin of SAP and the liver the excretory organ. This theory is based in part on experiments which showed that the removal of the abdominal viscera either singly or in combination did not substantially lower the level. Bodansky[16], on the other hand, has shown that alimentary hyperglycemia results in an increased SAP and that induced liver disease without obstruction has the same result. He postulates that the rise in SAP is of osseous origin in bone diseases and of hepatic origin in liver diseases. This is supported by Gould[41], who found that prolonged fat feeding increased the SAP. The level of SAP tends to remain at a more or less constant level from day to day, being unaffected by meals and incidental occurrences[94].

In animals, ligation of the common bile duct results in an increase of both SAP and intrahepatic AP without an increase of AP in any of the other viscera. Similar findings have been noted in obstructive jaundice in humans, with prominent accumulation of AP in the region of the bile capillaries. Three theories have been postulated to explain the increase of AP and SAP: (1) The enzyme accumulates because of decreased excretion in the bile. (2) The AP already present exhibits greater activity as the result of formation of an "activator substance" or a decrease in some "inhibitor substance." (3) There is an unusual formation of AP within the liver cells[35].

Reference may also be made to the observations that sera with high AP content from patients with obstructive jaundice and Paget's disease, as well as from dogs with experimental bile duct obstruction, are capable of augmenting the AP activity of normal serum when these are incubated together for 24 hours[24,33]. Similarly, when plasma from such dogs is injected into normal dogs, the elevation in SAP titer which ensues is higher than can be accounted for by adding the phosphatase activity of the injected plasma. In the dog experiments Cantarow and Miller[25] found very little of the infused phosphatase to be excreted in the bile. This suggested that a normally functioning liver does not actively remove phosphatase of this type from the blood and therefore contradicts the hypothesis that it originates in extrahepatic tissues.

Normal Values for SAP in Childhood. Talbot and associates have published the figures on SAP for 70 healthy children between 2 and 10 years of age[88,89]. The values ranged from 4.5 to 12 units by the Bodansky method. The average for the entire group was 7.2 units, and there was no apparent variation in relation to changes in age or between boys and girls. These values are essentially the same as those found by most workers, including Bodansky himself, and by common agreement are accepted by

most institutions as "normal." In infants under 1 month of age the plasma AP tends to be a little lower than in older infants and children[7,84].

Bodansky and Jaffe[17] were among the first to survey the levels of SAP in normal children and adults as well as in some of the diseases of the bones, using the Bodansky method. The average for 27 children was found to be 7.3 units per 100 cc., with values ranging from 3.1 to 13.1. Values from 10 to 13 units were common between the ages of 10 and 15 years. In about 300 other children between 1 and 15 years of age hospitalized for a variety of clinical conditions (excluding anemia, malnutrition, jaundice, and known diseases of bone) the range was approximately the same, from 5 to 14 units, with an average of about 7.5 units. A few of the infants in the first few months of life had values of 15 to 20 units. In contrast the average for adults was 3 units with a range from 2 to 4 units. There was relatively little variation in the values between 2 and 10 years of age. In a 16 year old boy with osteosclerosis fragilis generalisata (Albers-Schonberg disease) the SAP fluctuated from 15 to 21.5 units. High values were found in association with jaundice whereas anemia gave low values. The observations on the children, and on adults with a diversity of diseases, made it apparent that in diseases of the bone the serum phosphatase content becomes higher when there is extensive formation of abnormal bone or of osteoid tissue.

Josefsson[51], studying 50 normal infants under 2 years of age, noted that tests made in the summer gave higher values than in the winter. The mean values for SAP by his original micromethod were 180, with the highest and lowest values being 310 and 90. In contrast, with 32 premature infants weighing from 1030 to 2830 gm., the SAP ranged from 110 to 620. More than half were above the 300 reading. These higher SAP values did not correspond closely with the few signs of craniotabes and other evidences of rickets which were evident. The later development of the children did not show any relationship to the SAP levels. It was concluded that SAP determinations are without any real clinical value in the care of premature infants.

Vermehren[94] used an original micromethod to study SAP changes with ages. He too found somewhat lower values in the newborn period, with a rise at one month and an even greater rise at 2 months following which there was a slight decline to the first birthday and a further decline until 2 years of age. The values from then on were much the same from age 2 to age 10. In his scale the mean values for the newborn were 158, at 1 month 175, at 2 months 206, and 3 to 5 months above 235. The curves corresponding with increasing years ran identically for boys and girls until the 10th birthday. Above age 10 the girls showed slight elevation in the years age 10 to 13 years, while the boys had a slight drop at this time. Above age 13 the boys exhibited a rise whereas the girls in turn exhibited a drop.

Stearns and Warweg[84] have reported on the SAP values in 124 infants, children and young adults. The plasma content was low in the newborn, ranging from 0.1 to 0.2 (Kay method). At one month the mean unitage had risen to about the 0.5 level. At 4 and 6 months this was at the 0.3 level; at 12 months it was 0.25 and at 4 years it had fallen to 0.2 where it stayed essentially constant, until age 15 when it began to sink slowly to the adult level of slightly over 0.1 These figures were gathered from exclusively healthy children.

Tuba, Cantor, Siemens and Capsey[92] have reported on the findings of SAP among 108 school children aged 12 to

14 years in the neighborhood of Edmundton, Canada. Using a micromethod, important variations were found in SAP as related to sex, age groups, and season. For both children and adults the values for male subjects were appreciably higher than for females. The activity of the SAP was approximately 3 times greater among children than in a comparable series of 101 adults. The mean values in the spring were slightly higher for the boys than in the fall (13.5 vs. 12.8), whereas for the girls the values were 4.1 in the spring and 9.4 in the fall. The figures for acid phosphatase on these same children were 0.61 for the boys and 0.56 for the girls, this test being done only in the spring. There was a coincident slight decline in the level of serum inorganic phosphorus in the spring as compared with the fall.

Harrison and associates[46] have determined the level of AP in blood from 377 children aged 2 to 18 years, of whom 107 were studied in both fall and spring. Preliminary analysis showed the variations between duplicate determinations to be usually less than 0.4 nitrophenol units by the method of Bessey, Lowrie and Brach. Day by day tests on a number of children showed marked constancy with only 15% exceeding the maximum differences in duplicate analyses. The SAP levels ranged from 1 to 17 units, with a mean of 6.3 units. Approximately 84% fell between 4 and 9 units. Whether the values below 3 or 4 units were indicative of poor nutritional status could not be determined. Significant differences were not demonstrated between fall and spring in the 3 groups of subjects studied at both seasons, nor did the levels change appreciably during a 6-week period of "nutritional conditioning" in a health camp. Values indicative of active rickets in infants were not observed but a number of children had activity greater than 8 nitrophenol units, the arbitrary upper limit of normal suggested by Bessey. There is no evidence, however, that these mildly elevated values were in any sense related to disease states. The levels for boys and girls under the age of 10 years were similar. A group of children under 10 years of age who tended to be larger than others had mean SAP levels nearly 2 units higher than the others.

Adolescence. Differences between older boys and girls have been reported. Bessey (cited by Harrison[46]) determined SAP levels of over 1000 children of 11 to 18 years of age. He found that the values for the males reached the peak at about 14 years of age and then dropped, whereas the values for girls at 11 years were already decreasing. Bessey commented that the SAP changes during puberty were difficult to correlate with other data such as the rate of bone growth or the rate of weight change. For example, the SAP values in boys were already dropping at 13 years, an age at which the rate of bone growth is still rapid. Harrison and associates are inclined to attribute the difference between teenage boys and girls to sexual maturation[46]. The maximum average level in girls occurs approximately at adolescence, and then drops to the levels characteristic of the adult. The average for the boys drops much less rapidly, and many have high values through the seventeenth year.

*Bone Diseases.* Elevated values for SAP are generally recognized as associated with some disturbance of either the bones or the liver. Increases are often seen in bone diseases which involve formation of new bone tissue[50]. Among these are hyperparathyroidism, osteogenic sarcoma, Paget's disease, osteomalacia, and osteosclerosis fragilis generalisata (marble bones)[23]. Essentially normal findings are obtained in most cases of osteomyelitis, bone cysts,

achondroplasia, cretinism, and calcinosis universalis. Slight increases have been occasionally noted in cases of renal rickets.

One of the earliest workers to point out that the SAP is elevated in rickets was Smith[83] in 1933. Using Kay's method the plasma phosphatase in 60 infants with radiologic evidence of rickets ranged from 0.41 to 1.29 units with an average of 0.772 units. (Control normal infants had a range of 0.2 to 0.3 units.) Smith also noted that of 15 infants having various conditions associated with cessation of growth, including scurvy, marasmus and celiac disease, the SAP values were not elevated.

Stearns and Warweg[84] followed the SAP levels of 3 older children with late rickets. One was 3 years of age; the second, 12 years; the third, 12 years. The values for plasma phosphatase were elevated at first and decreased slowly with vitamin D therapy, though were probably still well above normal when roentgenologic healing was complete.

Bodansky and Jaffe[17] found the SAP to range between 20 and 190 units per 100 cc. in 21 children with rickets of varying degrees of severity. The values were highest in very marked rickets (58 to 190 units), less than 20 units in mild rickets, and normal in healed rickets. When vitamin D was given to cases of marked rickets the SAP level became stabilized in the high normal range and remained there for some months before dropping further. This was interpreted as indicating that the level remains elevated while active healing is in progress and does not drop to normal until bone reconstruction is complete.

The most careful study of the relationship between SAP and rickets was that of Klasmer[57], who found the mean value of SAP in 320 healthy children between 6 months and 2½ years of age to be 9.4 units (Bodansky), with a normal range of 5.6 to 15.0 units. Sex and age did not influence the results. Fifty-five similar infants with active rickets were studied; the SAP in this group was elevated in all but a few. In most of these the readings were above 20 units. Parallelism was pronounced between the severity of rickets and the increase of phosphatase activity. In 500 other children with miscellaneous conditions, including many who were apparently well, an increase in SAP was found in seventeen. Two of these had subclinical jaundice, and the third had severe bone decalcification. The 14 other children had increased SAP (mean: 16.8 units) but dubious clinical signs of rickets at the first examination. Subsequent studies indicated that these children were suffering from rickets. Clearcut acute swelling of the epiphyses was almost always accompanied by increased SAP. Indefinite changes in the epiphyses were usually not a sign of active rickets; the mean value for SAP in 36 such cases was 10.77 units and roentgenograms also showed no active rickets. "When increased phosphatase activity is present, with insufficient or completely lacking clinical indications of rickets, a roentgenogram or repeated determinations of the phosphatase activity would show rickets as the cause. The phosphatase activity of the serum remains high throughout the period of active rickets; the decrease to normal values coincides fairly well with clinical recovery, while increase values for phosphatase activity may precede the first clinical symptoms[57]." In Klasmer's hands, as with most other workers, the determination of serum phosphorus is much less reliable as a diagnostic sign of rickets.

Klasmer found an interesting variation in the mean value for SAP in relation to seasons of the year. The levels for the control groups of 320 healthy children and for 625 other children

with poor development showed values which were more than 1.5 units higher in the winter than in the fall. The values for spring and summer were intermediate between those for winter and fall. This was interpreted as indicating that the SAP level is an indirect test for vitamin D; that there is a climax of saturation with vitamin D at the end of summer and a relative lack during winter even in children without any signs of rickets. It may be commented in passing that studies on the incidence of rickets must always differentiate between active rickets and healed rickets. Klasmer has attempted this differentiation. Most other workers have not.

Barnes and Carpenter[6] have reported on 187 infants with clinical signs of rickets and histories of low or absent vitamin D intake. Using the criterion of 12.5 mg. phosphatase per cc. as top normal, they found that 65.2% of the infants with rickets had SAP values above this level. They noted also that the level tended to subside as treatment was given, the average time for reaching normal being about 2 months.

Yieh and Wissler[102], using Bodansky's method, found the SAP in 17 children with severe rickets to range from 14.5 to 57 units, with a mean of 28.4. In 15 milder cases the range from 7.2 to 16 with a mean of 11.2. Interestingly, there were two children with fever and rickets in whom the phosphatase levels seemed displaced downward.

Barnes, Munks and Kaucher[8] investigated SAP as an indicator for recovery in rickets. They found 798 infants in the child welfare clinic of Detroit over a 6 year period who were considered possibly rachitic. Of these, 199 had an SAP level of 20 units or more, which was deemed to be sufficiently above normal to be indicative of rickets. Forty-eight of these infants were divided into groups according to phosphatase ranges and treated with vitamin D in cod liver oil or tuna liver oil at dosage of 600, 900 and 2400 I. U. of vitamin D daily. Each of these liver oils at all 3 medication levels caused significant drops in SAP by the sixth week and all but one by the fourth week. When the various groups were later compared, no significant differences were found in the relative degree of SAP reduction during the first 6 weeks of treatment.

Josefsson[51] has recorded the response of SAP to the so-called "shock" or massive single dose therapy of rickets, employing an original micromethod. The SAP was raised in 3 children with severe rickets, in all but 1 of 8 children with moderate rickets and in only 5 of 26 children with mild rickets. Comparative studies with blood phosphorus indicated that the SAP is a better criterion for the presence of rickets than is the low blood phosphorus. Of 21 infants with increased SAP given the massive dose treatment, the values for SAP remained high for at least 12 to 14 days afterwards in all with true rickets and fell to normal within 10 days in the remainder. It was concluded that if the values continue high after treatment or fall at a slow rate the rickets is more severe.

Van Creveld and Mastenbroek[93] described studies on both acid and alkaline phosphatase in rickets following injections of one single dose of 500,000 international units of vitamin $D_3$ as treatment for rickets. In 3 infants followed serially from the beginning of treatment the SAP dropped from abnormal to normal levels or to top normal levels, whereas the acid phosphatase showed a rise which reached a maximum 3 to 5 months after the injection of vitamin $D_3$. By the King-Armstrong method the peak values were 14, 10.1 and 12 units respectively, as compared to more normal values in these children of 3.8 to 4.2 units. The curves for the 2 sorts of phosphatase

did not run parallel. The blood phosphorus level was abnormally low in these children at the beginning but promptly rose to normal range. In none of these children was there abnormal or increased values for calcium, cholesterol or inorganic phosphorus after the injection of $D_3$.

Saggese, De Luca and Daffi[78] also reported on the effects of single large doses of vitamin D on recovery of rickets. Using the King-Armstrong method they noted elevated SAP in 39 infants aged 9 to 36 months with rickets. The range was from 22 to 28 in mild cases to 21 to 88 in the severe cases. Following the injection of 20,000 to 50,000 I. U. of vitamin $D_2$ in a single dose the SAP declined by 1.5 to 27 units.

*Scurvy.* Schwachman and Gould[79] studied the SAP in 18 infants with "unequivocal" scurvy, aged 7 to 13 months. The average value of serum phosphatase on admission to the hospital was 3.2 Bodansky units with a range of 1.1 to 4.9 units, as compared with the mean value for normal infants of approximately 7.2 with a range from 4.5 to 12 units. A substantial rise in this low level became apparent within a week following the institution of vitamin C therapy, even though vitamin D was withheld for the time. The SAP after 7 to 29 days of treatment ranged from 8 to 19 units. The rise was greatest in the child with extensive subperiosteal hemorrhages.

*SAP in Nutritional Surveys.* Youmans and associates[103] have described the results of a nutritional survey of a rural population in middle Tennessee with respect to vitamin D and calcium status. Three of 224 white children and 8 of 178 colored children had SAP values above 12 units (Bodansky). There were 12 other children under 12 years of age who had SAP activity above 12 units. None of these had rickets. Only 2 were infants, the others being 5 to 13 years of age. Seven came from 3 families. Only 1 had received any vitamin D supplement and that only for 6 weeks. It is suggested that an elevated SAP in children above 3 years of age reflects vitamin D or calcium deficiency, or both. A total of 66 children under 15 years of age in the white group, and 49 in the colored group, had Bodansky units in the range from 8.0 to 11.9. These figures were interpreted as being "normal" but it is not impossible that some of these values represent an increase above normal. Clinical and laboratory indications of calcium deficiency were uncommon. The incidence of diagnosed rickets, on the basis of the other criteria in this study—physical examination especially of the skeleton, signs of tetany, roentgenograms of some of the bones, and phosphatase, phosphorus and calcium concentrations in the blood—indicated that evidences of rickets were present in about 25% of the subjects under 3 years of age, though in many of these the disease was probably healed. What makes surveys for calcium or vitamin deficiency so difficult is that there are few symptoms and signs except in the relatively severe or advanced deficiency states. It is unfortunate that in this survey the phosphatase test was done with only a few of the younger subjects who had clinical signs of rickets.

In August 1944 a survey was made by Adamson and associates[1] of the nutritional status of the population of Newfoundland, especially in the city of St. John's and several nearby ports. The general conclusion was that the nutritional status of the people in general was poor, inasmuch as evidence of lack of vitamin A, riboflavin and ascorbic acid was seen with great frequency. Phosphatase studies were carried out on many of the individuals. Nearly all the values for both children and adults were within normal limits. With the method of Bessey, Lowrey and Brock[11],

the mean level was 4.9 units for children under 18 years of age and 1.9 units for adults above 18 years of age. Only 4.9% of the children had values higher than 8 units taken as the top normal and only 1.9% of the adults were above 3 units which is the value of top normal for adults. It was concluded by the authors that these findings indicated, in general, an absence of vitamin D deficiency within the population.

*Hypothyroidism.* Talbot[87] applied the phosphatase test to the study of patients with hypothyroidism, following the observation by Bodansky and Jaffe[17a] that a girl cretin 4 years of age with a normal SAP showed a rise after thyroid treatment. The original levels for 4 out of 5 such untreated children were unusually low (average 3.0 Bodansky units). These children ranged in age from 3 months to 10 years. After several months of thyroid therapy the levels of SAP were restored to normal (average 8.5 Bodansky units).

Talbot and associates[88,89] later described the SAP values in 30 infants and children with cretinism and juvenile hypothyroidism. In 12 of these the levels were studied before thyroid therapy. The value for SAP was lower than 4.5 units per 100 cc. for 11 of these untreated patients and at 6.0 for the 12th patient. In contrast, these and other patients after receiving thyroid therapy had SAP values coinciding with the normal range (Bodansky). The values later diminished again when thyroid therapy was reduced or discontinued. Lower levels of SAP were not observed in diseases which might be confused with juvenile hypothyroidism or cretinism, with a possible exception of a few cases of idiopathic dwarfism. The average value for SAP in 8 children with idiopathic dwarfism was 6.6 units (range 4.5 to 9.0 units). Mention is made of the fact that in some cases of scurvy, severe malnutrition, severe anemia, arthritis, achondroplasia, splenomegaly and abdominal tumors there may be a lowering of the SAP. Bixby[13,14] concluded that the levels of SAP were normal in mongolism. Talbot[89] concludes that SAP is useful as an index of thyroid function in children, provided the other diseases which may cause a lowering of SAP are excluded.

Hill and Weber[48] have reported on studies of 23 children showing obvious retardation in development and low basal metabolic rate due presumably to hypothyroidism. The children ranged in age from the newborn period to 13 years. These 23 children showed symptoms of mild hypometabolism clinically, and, in addition, either marked osseous retardation or low metabolic rates. Twenty of the 23 children had SAP values of 5.6 Bodansky units or less. The 3 others had values between 6.4 and 6.8 units. In 14 out of 16 control children the range was 5 to 9.7 units. Two children with normal osseous development and low SAP had minor symptoms suggestive of hypothyroidism. After receiving thyroid therapy for one month as a therapeutic test, they showed clinical improvement along with increased values of SAP approaching the normal range. Hill and Weber conclude that as much or more information can be derived from the SAP determination than from the serum or plasma cholesterol tolerance test in mild hypothyroidism. The chief advantage to the SAP test is its comparative simplicity and lack of expense.

*Liver Disease.* In adult patients with jaundice it is often thought that complete obstruction of the common bile duct is usually associated with a marked increase in SAP, whereas hepatitis may or may not induce such an increase. The fact that adults with incomplete obstruction may exhibit an increased SAP without any increase of serum bilirubin is attributed to less efficient

permeability of the kidney to phosphatase as compared with permeability to bilirubin[44].

Rapoport[73] has presented observations on 15 children on whom determinations of phosphatase, along with other tests of liver function, were obtained in the early stages of infectious hepatitis. There were 13 children, ranging in age from 7 to 14 years. Eight of the children were examined the day after the jaundice was first noted, and the others within the first week of jaundice. One of these was diagnosed as having hepatitis without jaundice. Each child showed a slight elevation in the SAP at the time of first testing, the values ranging from 14 to 37 units (Bodansky). These elevations were transient, and as a rule fell to normal within a week. There was no appreciable parallel between the rise in SAP and the rise in serum bilirubin. This was interpreted as indicating that a rise in SAP during hepatitis reflects a stimulation in the formative activity of the liver rather than a suppression of its excretory activity. The author suggests that the more frequent incidence of increased SAP in obstructive jaundice may be due, at least in part, to a stimulation by biliary obstruction upon formation of phosphatase by the liver cells. Reference is made to the observation by several workers that infants with congenital atresia of the bile ducts may have only a moderately increased SAP, if any at all. Rapoport suggests that in such patients, if the "retention" theory be correct, high levels of SAP would obtain. The fact that there is no appreciable increase indicates that the element of retention, at least in this type of obstructive jaundice, plays only a minor role.

Payne comments that in 54 children with jaundice, usually of the infectious type, the SAP was often elevated, especially in the early stages[71]. There was no parallelism between the SAP and bilirubin level or the clinical course. While it is difficult to draw many conclusions from a single test of SAP, Payne suggests that children with mild infectious hepatitis should not be regarded as cured if the phosphatase has not yet returned to normal.

Gall's observations in infectious mononucleosis may be mentioned in this connection[36]. Gall performed SAP tests on 34 patients with infectious mononucleosis (all adults) and found significant elevation in all but one instance. The readings ranged from 8 to 44 Bodansky units (top normal for adults: 4 units). This elevation was attributed to altered liver function, the reasons being that anatomic lesions have been found in the liver in the rare case of infectious mononucleosis available for such study and abnormal results were also shown in other liver function tests carried out with these same patients.

Miscellaneous. SAP has been found to be elevated in a case of epiphyseal dysgenesis[15]. Yieh and Wissler[102] found SAP to be normal in children with renal rickets and hyperphosphatemia whereas it was raised in the hypophosphatemic form of the Fanconi syndrome. This was substantiated by McCune[66] and workers who found an elevated SAP in a case of intractable hypophosphatemic rickets. Gill[37] has reported studies on 3 children and 1 adult with vitamin resistant rickets. The 3 children all had markedly elevated SAP whereas the adult who was the mother of 2 of the children had normal SAP. Gunther[43] found that the SAP was normal or slightly elevated in a case of rickets resistant to vitamin D therapy but increased sharply on administration of higher doses of vitamin D. SAP was normal in multiple cystic tuberculosis of the bone[64] and depressed in osteopetrosis[26], osteochondrodystrophy deformans[30] and in a peculiar osseous disease characterized

by areas of increased bone density and dilatation of the bone shaft[76].

SAP has been found depressed in a case of progeria[89] and in the post-acidotic state of infantile diarrhea[74]. Of 11 children with celiac and celiac-like disease, 7 had subnormal values, 1 with a reading of 2.2 units[102]. One child with uremic vomiting gave a reading of only 2.4 units[102]. It was normal in both diabetic[97] and pituitary dwarfism[21].

Mason and Henderson[65] found a normal SAP in a case of glycogen storage disease. Another case of glycogen storage disease was reported to have a reading of 15.4 units on one occasion and later 2.4 units[102]. In 2 children with osseous dystrophy following icterus gravis neonatorum, Braid[19] noted increased SAP in association with the bone changes and evidence of liver dysfunction. In these cases the bone dystrophy was ascribed to the failure of the liver to store and utilize vitamins.

Of 6 patients with anemias of various sorts (1 with Cooley's anemia), 4 had subnormal values (2.0 units or less) and 2 others had low normal values (4.0 to 4.8 units)[102].

CONGENITAL "HYPOPHOSPHATASIA." Rathbun[74a] has described the extraordinary case of a deformed newborn infant whose bones exhibited lack of calcification and marked epiphyseal enlargement, along with almost absent SAP during life and comparatively negligible amounts of extractable AP in the bones and other tissues after death at the age of 2 months. The vault of the skull was almost devoid of calcium. The low to absent AP was believed to be the primary defect responsible for the clinical picture and the coined term "hypophosphatasia" was applied to it. The case report gives no information with respect to the acid phosphatase content of blood and tissues or to any histologic studies with special stains for the phosphatases.

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PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 15, 1949

**The Effects of Jet Engine Noise on the Cochlear Response of the Guinea Pig.** IRVING E. ALEXANDER, Ph.D., and FREDERICK J. GITHLER, A.B. (Dept. of Psychology, Princeton Univ.). This work was carried out in the Princeton Psychological Laboratory, with the cooperation of the Naval Air Experimental Station, Aeronautical Medical Equipment Laboratory, Captain J. R. Poppen, M. C., commanding, under contract with the Office of Naval Research, as Contract N6-onr-270, Task Order III (Project NR 145-322) and Bureau of Medicine and Surgery, NM 003-037. Cochlear potentials were measured at various time intervals for 4 groups of guinea pigs after a 15 minute exposure to jet engine noise. A control (non-exposed) group was also tested. The findings are as follows: 1. Exposure to the jet engine noise results in auditory impairment throughout the frequency range. 2. Partial recovery occurs progressively up to 3 weeks following the exposure. 3. After injury, the cochlear potentials are further impaired on the presentation of even moderately intense sounds. The exposed ear has been rendered unusually susceptible to further injury. 4. There is preliminary evidence that indicates the possibility that further degeneration occurs between 3 and 6 weeks after jet stimulation. 5. Results based on a limited sample disclose that protected ears show no immediate effects in auditory acuity. However, after a period of 6 weeks some deterioration is observed.

Tentative explanations of the results are offered, and recommendations are made for concerned personnel.



**Simultaneous Comparisons of Alveolar Gas Tensions Obtained by Various Sampling Methods.** E. S. BARKER, M.D., R. G. PONTIUS, M.D., D. M. AVIADO, M.D., and C. J. LAMBERTSEN, M.D. (Dept. of Pharmacology, Univ. of Penna.). $PO_2$ and $pCO_2$ of alveolar gas was determined for samples obtained simultaneously by various methods: 1, Haldane-Priestley end-expiratory; 2, Rahn (continuous, end-normal expiratory, from beyond mouth); 3, Tracheal (continuous, end-normal expiratory, from a catheter introduced through the crico-thyroid membrane to the tracheal bifurcation); 4, "Effective" method of Riley *et al.* (calculation based on expired gas, blood $pCO_2$ and expired gas R.Q.); 5, Alveolar Equation of Bohr (calculation by correcting expired gas for the effect of the dead space. Several representative dead space values were used). Expired gas was collected in a Tissôt gasometer. All gas samples were analyzed with the Scholander .5 cc. gas analyzer. Gas tensions of arterial blood, collected simultaneously and analyzed by a direct microtonometric method (modified after Riley *et al.*), were compared with the alveolar tensions.

Measurements were made on 11 resting, normal, young, adult males. Samples were collected during 3 experimental periods of 2 minutes on each subject. The state of relaxation was observed by the constancy of alveolar $pO_2$ determined with a Pauling tensimeter by the Rahn method. The results are summarized in Table 1.

The variability for each method due to variation between different individ-

uals and that due to repeated measurements on the same individual has been determined statistically.

An analysis was made of the statistical differences between individual measurements obtained by the various methods. For $pO_2$ there was a statistically significant difference between all comparisons except: 1, Haldane-Priestley and arterial blood; 2, Effective and Haldane-Priestley; and 3, Effective and Tracheal (these 2 show the smallest difference).

For $pCO_2$ there were no statistically significant differences except that the Rahn differed from each of the other values. (Since they are not independent values, the alveolar equation calculations were not included in these comparisons.)

The significant difference between the Rahn and the Tracheal, although both were measured simultaneously at the same phase of respiration, suggests that an ordinary normal expiration is not sufficent to wash out the dead space.

The fact that the Tracheal and the Effective methods show the closest correlation and that these 2 methods are entirely independent is indirect evidence in favor of values obtained by these methods.

The Tracheal method was introduced as a means of evaluating other methods. Although no serious difficulties were encountered, the method is not considered practical for routine use.

TABLE 1.—ALVEOLAR AND ARTERIAL GAS TENSIONS

| Sample or Method | $pO_2$ Mean | $pO_2$ Std. Dev. | $pCO_2$ Mean | $pCO_2$ Std. Dev. |
|---|---|---|---|---|
| Arterial Blood | 96.6 | ±4.1 | 40.5 | ±4.4 |
| Haldane-Priestley. End-Expiratory | 98.0 | ±5.6 | 40.6 | ±3.2 |
| End-Inspiratory | 104.3* | ±5.7 | 38.7* | ±3.5 |
| Mean | 101.2* | ±5.7 | 39.7* | ±3.8 |
| Rahn *et al.* | 103.1 | ±4.1 | 38.6 | ±2.4 |
| Tracheal | 99.7 | ±3.9 | 40.4 | ±2.9 |
| Effective (Riley *et al.*) | 100.3 | ±5.5 | 40.5** | ±4.4 |
| Alveolar Equation. D.S.=.3 X Tidal Vol. | 99.6 | ±4.1 | 42.0 | ±3.4 |
| D.S.=150 cc. | 97.6 | ±7.1 | 43.3 | ±5.1 |
| D.S.=180 cc. | 91.8 | ±10.6 | 48.2 | ±7.4 |

* From a later series (25 measurements on 13 normal resting men).
** Effective $pCO_2$ is assumed to equal arterial blood $pCO_2$.

**Isotopic Studies of the Biosynthesis of Nucleic Acid Components. I. Purines and Pyrimidines.** MILTON R. HEINRICH*, Ph.D., D. WRIGHT WILSON, Ph.D., and SAMUEL GURIN, Ph.D. (Dept. of Physiological Chemistry, School of Medicine, Univ. of Penna.). Carbon dioxide, acetic acid, and glycine have been studied as possible precursors of the nitrogenous bases of nucleic acids and nucleotides in the rat. The compounds, labeled with radioactive carbon, were administered to rats, followed by isolation of the purines and pyrimidines from the tissues, and assay of their radioactivity. Nucleotides were first extracted from the carcasses with cold trichloroacetic acid, hydrolyzed and adenine isolated. After removing lipids from the remaining tissue, the nucleic acids were extracted with hot 10% sodium chloride, and hydrolyzed to individual purines and pyrimidines.

After hourly injections of labeled $NaHCO_3$ into a rat for 7 hours, a small amount of isotope was found in the adenine of the nucleotides and in the adenine, guanine and uracil of nucleic

* National Institutes of Health Postdoctoral Research Fellow.

acids. The isotope was shown by means of permanganate degradations to be in the non-ureide carbon of guanine and the ureide carbon of uracil. Carboxyl-labeled sodium acetate, injected into rats for 5 days, gave approximately the same degree of incorporation; no isotope appeared in the ureide or guanidino carbons of guanine.

Excellent incorporation into the purines was observed when glycine labeled in the carboxyl group was fed to rats for 10 days. The isotope concentration was approximately equal in nucleic acid guanine and adenine, and slightly higher in nucleotide adenine. To determine the position of the isotope in the nucleic acid guanine, a sample was hydrolyzed with concentrated HCl at 200° to give glycine in which the carboxyl carbon is known to be derived from carbon 4 of guanine. The carboxyl of this glycine, obtained as $CO_2$ by treatment with ninhydrin, contained essentially all the isotope present in the guanine.

**Nucleic Acids and Antibody Production by Plasma Cells.** CAROLYN FORMAN, M.D., D. L. DRABKIN, M.D., and W. E. EHRICH, M.D. (Depts. of Pathology and Physiological Chemistry, Grad. School of Medicine, Univ. of Penna., and the Phila. General Hospital.) Rabbits were injected with typhoid antigen into each foot pad, and the formation of antibody was compared with the changes in nucleic acids in the popliteal lymph nodes. Desoxyribose nucleic acid (DNA) and ribose nucleic acid (PNA) were determined by the method of Schneider as adapted by Drabkin. Sections of the nodes were stained with methyl green and pyronin.

It was found that DNA increased immediately with the weight of the node, whereas the peak of PNA increase occurred between the 4th and 6th day after vaccine injection when antibody formation is at its maximum. A study of sections revealed that during the first 6 days of the experiment the cellular reaction was chiefly that of plasma cells. Most of the PNA was contained in the plasma cells. The lymphocytes began to proliferate in significant numbers on the 3rd and 4th day, and germinal centers began to appear on the 4th and 5th day. They showed their greatest activity on the 9th day when PNA and antibody formation had passed their peaks. These results are interpreted as indicating that the plasma cell and not the lymphocyte are responsible for antibody formation.

**The Standardization of Hemoglobin Measurement.** DAVID L. DRABKIN. (Dept. of Physiological Chemistry, Grad. School of Medicine, Univ. of Penna.). A simplified, reliable procedure for the standardization of hemoglobin measurement, with hemoglobin iron as the ultimate basis of reference, has long been needed. There is now convincing evidence that the spectrophotometric or photometric determination of cyanmethemoglobin, MHbCN, is the most direct analysis available for total hemin or hemoglobin iron[1]. Tedious and exacting standardization procedures may be circumvented in the calibration of commonly used photoelectric filter photometers for the accurate measurement of hemoglobin concentration. This is done by employing established ratios of optical density, $\bar{D}$, at a suitable wave-length (green spectral region; filters with maximum transmittancy at 540 $m\mu$ and at specified concentrations, for MHbCN or for oxyhemoglobin, $HbO_2$, and a standard solution of cupric ammonium sulfate, Cu, prepared gravimetrically and volumetrically[2] from a good grade of commercial cupric sulfate, $CuSO_4\ 5H_2O$. Such calibration ratios or factors are: $\bar{D}_{MHbCN}/\bar{D}_{Cu} = 1.020$, $\bar{D}_{HbO_2}/\bar{D}_{Cu} = 0.963$ (applicable to the Klett-Summer-

son photometer), and 0.857 and 0.890, respectively (applicable to the Evelyn instrument). The factors were established for hemoglobin at a concentration of 0.0358 mM/L (0.0598 gm./100 ml., *i. e.*, blood, originally containing exactly 15.0 gm. of hemoglobin per 100 ml., diluted 1:251) and for the copper standard at a concentration of 0.012 M/L. An example of the use of the ratios follows: in a Klett-Summerson photometer, the copper standard yields $D_{Cu} = 206$. On this instrument, a blood sample, originally containing exactly 15.0 gm. of hemoglobin per 100 ml., diluted 1:251 (and converted to MHbCN), would give the value 210 for $D_{MHbCN}$ (from $D_{Cu}$ x established factor, or 2.06 x 1.020). This simple procedure effectively calibrates the instrument for hemoglobin measurement.

It has appeared desirable to go a step beyond this procedure, and provide a relatively permanent glass standard. For this purpose a stable, Corning blue glass filter, f, No. 4305, 4.2 mm. thick, cut into appropriate size and shape, and suitably mounted in metal jackets for adaptation to the Klett-Summerson or Evelyn instruments, has been employed. For these particular filters, as an example, $D_{Cu}/D_f = 1.190$. $D_{Cu}/D_f$ is, of course, obtained from the determined values of the copper standard and standard glass filter for each instrument. In this case, $D_{Cu} = 206$, $D_f = 173$, and, hence, $D_{Cu}/D_f = 1.190$. Now, since the established factor, $D_{MHbCN}/D_{Cu} = 1.020$, $D_{MHbCN}/D_f$ must equal 1.020 x 1.190, or 1.214.

In using a new glass filter, it must either be pre-calibrated, *i. e.*, the $D_{MHbCN}/D_f$ or $D_{HbO_2}/D_f$ ratios must be furnished, or the glass must be calibrated against the copper standard, as above, and the hemoglobin to glass factor obtained from the established ratios of $D_{MHbCN}/D_{Cu}$ or $D_{HbO_2}/D_{Cu}$. Both the copper solution and calibrated glass serve as desirable instrumental performance standards, to be used periodically, as well as for the calibration of the instrument for hemoglobin measurement. The same method has broad photometric applicability, and may be suggested for many other methods, besides hemoglobin.

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# BOOK REVIEWS AND NOTICES

ACCLIMATIZATION IN THE ANDES. HISTORICAL CONFIRMATION OF "CLIMATIC AGGRESSION" IN THE DEVELOPMENT OF ANDEAN MAN. By CARLOS MONGE, M.D., Univ. of San Marcos, Lima. Translated by Donald F. Brown, Ph.D. Introduction by ISAIAH BOWMAN, Johns Hopkins Univ. Pp. 130. Balt.: Johns Hopkins Press, 1948. Price, $2.75.

THE content of this small book is well expressed in its subtitle. The author, a scientific physician and former Dean of the Medical Faculty at Lima, has for many years studied "climatic aggression" (*i.e.*, the effects of "air temper") on Peruvian coastal dwellers and Andean uplanders. (The word "air-temper" is a valuable adaptation of the "temple" of the old Spanish chroniclers, used to indicate the general state of the air—temperature, humidity, atmospheric pressure, etc.) The author makes a vigorous plea for the use of the knowledge gained to improve the physical condition of Peruvians. E. K.

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PRACTICAL ASPECTS OF THYROID DISEASE. By GEORGE CRILE, JR., M.D., Cleveland Clinic. Pp. 355; 101 ills. Phila.: W. B. Saunders, 1949. Price, $6.00.

DRAWING from his experience in the surgical treatment of approximately 1000 patients with diseases of the thyroid, the author presents a concise, lucid treatise on thyroid disease. The mode of action and present status of the anti-thyroid drugs in the treatment of hyperthyroidism is discussed and there is a detailed account of the preoperative and postoperative care and technic of thyroidectomy. A large section of the monograph is devoted to malignant tumors of the thyroid.

Owing to controversial opinions currently existing, the author's views relating to such problems as the use of the anti-thyroids in the treatment of hyperthyroidism, the value of radioactive iodine, and the treatment of cancer of the thyroid may not be generally acceptable, but he acknowledges the fact that sufficient time has not yet elapsed to evaluate completely the newer forms of therapy. The importance of having a team of specialists skilled in surgery, internal medicine, Roentgen therapy, and nuclear physics in studying thyroid disease is stressed. I.R.

## NEW BOOKS

*Nursing of the Sick—1893.* By ISABEL A. HAMPTON and Others. Pp. 218. New York: McGraw-Hill, 1949. Price, $3.50.

*Neurological and Neurosurgical Nursing.* By C. G. DE GUTIERREZ-MAHONEY, M.D., Assoc. Prof. of Neurology, Vanderbilt Univ. School of Medicine, and ESTA CARINI, R.N., B.S., Neurological Inst., Presbyterian-Columbia Medical Center, New York. Pp. 516; 51 ills. St. Louis: C. V. Mosby, 1949. Price, $5.75.

*Thyroid Function as Disclosed by Newer Methods of Study.* Edited by J. H. MEANS, and 12 Others. Pp. 229; illustrated. Ann. New York Acad. Sci., **50**, 279-508, 1949. Price, $3.00.

*Safer Ways in Nursing.* By JOINT TUBERCULOSIS NURSING ADVISORY SERVICE. Pp. 108. New York: National Tuberculosis Assoc., 1948. Price not given.

*British Encyclopaedia of Medical Practice. Medical Progress, 1949.* Edited by RT. HON. LORD HORDER, Physician to the King. Pp. 431. London: Butterworth & Co., Ltd., 1949. Price not given.

As in earlier volumes, Medical Progress is treated under Critical Surveys (121 pages covering 12 fields of medicine); Drugs, the British Pharmacopoeia 1948 (17 pages) and Abstracts, ranging from Abdominal Pain through Whooping Cough (250 pages).

*Medical Clinics of North America.* Nationwide Number. Pp. 313; 30 ills. Philadelphia: W. B. Saunders, March, 1949. Price, $15 a year.

This volume presents a symposium on treatment of long-term illness. It discusses such subjects as hypertension, vascular diseases, heart failure, tuberculosis, non-tuberculous lung diseases, asthma, diabetes, blood dyscrasias and other chronic problems. Most of the presentations avoid quoting experimental work and confine themselves to practical clinical discussions. There are excellent articles on Chronic Illness and the Constitutionally Inadequate, Mastery of Long-Term Illness, Planning for Long-Term Illness and The Patient with Long-Term Illness as a Surgical Risk. This volume maintains the high standards of this series. H. H.

*Introduction to the Szondi Test.* By SUSAN DERI. Foreword by DR. LIPOT SZONDI. Pp. 354; 19 figs. New York: Grune & Stratton, 1949. Price, $5.00.

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